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MEASUREMENT OF SELECTED PULMONARY PARAMETERS IN PATIENTS WITH BRONCHIAL ASTHMA WITH AN EVALUATION OF ADRENALINE AND ISOPROTERENOL

BY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Measurement of Selected Pulmonary Parameters in Patients with Bronchial Asthma with An Evaluation of Adrenaline and Isoproterenol" submitted by Ahmad R. Esfandiary in partial fulfilment of the requirements for the degree of Master of Science.

ABSTRACT

An assessment of the response of 22 asthmatic and 5 normal subjects to the inhalation of 15 breaths of Isoproterenol (Isuprel) and of Adrenaline was made. Measurements of the diffusing capacity of the lung (DL), the membrane diffusing capacity (DM), pulmonary capillary blood volume (Vc), pulmonary parenchymal tissue volume (VT) and pulmonary capillary blood flow (Qc) were carried out before and after drug administration in each subject.

Diffusing capacity measurements were made by the single breath technique as modified by Ogilvie.[94] The two components of the diffusing capacity (DM and Vc) were measured by a determination of DL at low and high oxygen tensions followed by a mathematical solution of the equation $\frac{1}{DL} = \frac{1}{DM} + \frac{1}{\theta Vc}$ as derived by Roughton.[105] Acetylene was used as the indicator gas for the measurement of Vt and Qc.

A computer program in "APL" was developed to facilitate the necessary calculations and to ensure precision and reproducibility in the

techniques of computation.

The values for diffusing capacity (DL) were smaller in the asthmatic than in the normal individuals. ($P < 0.02$) We demonstrated no significant change in any of the above mentioned parameters in either normal or asthmatic individuals following administration of either Adrenaline or Isoproterenol.

Although it may be that Adrenaline and Isoproterenol in the dosage administered caused no appreciable change in this group of subjects it seems more likely that the technique itself is not appropriate to delineate the type of alteration occurring. Because the testing must be carried out over a time period of several hours, the basic assumption that base line conditions are stable is not valid. In addition this technique depends so importantly on ventilation perfusion relationships that changes in ventilation and blood flow could conceivably have cancelled themselves out.

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STATEMENT OF THE PROBLEM

INTRODUCTION

Bronchial asthma is a common disease, ranking high among the causes of disability in America and Europe. It is chronic in nature and is characterized clinically by episodic bronchial obstruction and ventilatory insufficiency, by wheezing respiration, dyspnea, cough and mucoid sputum production.

The essential pathological features of air ways in bronchial asthma are: mucosal edema, hypersecretion of a viscid, tenacious mucus and smooth muscle contraction. Clinically two types of bronchial asthma are recognized; firstly, intrinsic asthma, the pathogenesis of which is poorly understood, and secondly, extrinsic asthma for which the underlying immunological, biochemical and pharmacological mechanisms are reasonably well defined[87].

Although the chain of events leading to intrinsic variety remains obscure, both types of asthma share essentially the same physiological and pathological features.

Functionally, characteristics of bronchial asthma are: low maximal breathing capacity and forced expiratory volume. There is a decrease in dynamic compliance as well as an increase in air way resistance and work of breathing. All observers have reported some degree of reduction in vital capacity with evaluation in residual volume and functional residual capacity[9].

Evaluation of the pulmonary diffusing capacity has proved to be difficult and because of methodological differences and variations in technique, variable results have been reported by different groups

of investigators. With the introduction of cardiac catheterization and recent application of gas chromatography in respiratory physiology certain aspects of pulmonary hemodynamics have been studied. However it seems that the state of knowledge in this area at present time is still poor.

THE PROBLEM

Diffusing capacity of the lung is viewed as the single pulmonary function test which is usually used to differentiate bronchial asthma from pulmonary emphysema.

Diffusing capacity in bronchial asthma has been reported variably from below to above normal, with values around the predicted level in most patients with pure bronchial asthma.

Differences in technique of measurement and variations in patient material are stated to be the main reasons for this variability.

Although a fair amount of information is now available pertaining to diffusing capacity, the literature shows that pulmonary hemodynamics in bronchial asthma has been less well studied.

Published reports of the tissue volume of lung in asthma are scarse. Measurement of pulmonary parenchymal tissue volume would further clarify the quantitative aspect of parenchyma of the lung which in pure bronchial asthma, at least theoretically, is expected to be intact.

DELIMITATION OF THE STUDY

The parameters measured consist of:

1. total lung diffusing capacity (DL)
2. membrane component of diffusing capacity (DM)
3. pulmonary capillary blood volume (VC)
4. pulmonary parenchymal tissue volume (VT)
5. pulmonary capillary blood flow (QC)

The effect of inhalation of Adrenaline and Isoproterenol - the most commonly used bronchodilators in therapeutic dosages on the above pulmonary parameters are evaluated.

LIMITATION OF THE STUDY

Study of the pulmonary hemodynamics is limited to the measurement of the pulmonary capillary blood flow and pulmonary capillary blood volume. Because of the nature of the study pulmonary artery and pulmonary capillary pressures are not obtained.

In those patients who are smokers and may not follow the instruction regarding temporary abstinence from smoking, carbon monoxide back pressure in the pulmonary capillary may hinder diffusion of this gas across the alveolo-capillary membrane and falsely decrease the value for diffusing capacity of the lung.

Because the expiratory sample is obtained following the elimination of the initial 1300 milliliters of the expirate, it is obvious that single breath technique can not be applied to evaluate the above mentioned parameters in patients with very severe bronchial asthma who may have vital capacities below this level.

As differentiation of bronchial asthma from other non specific chronic lung diseases by clinical criteria alone is not adequately accurate, asthmatic patients who may have associated mild to moderate emphysema may have been inevitably included in the patient sample and consequently the results have been modified accordingly.

As most of the measurements of the stated cardio-pulmonary parameters are done on patients during a completely symptom free interval, or while in a steady state in partial remission, the results of this study determines the more chronic patho-physiological effects of bronchial asthma.

Finally, with all existing methods for diffusion capacity measurement, the imbalance of ventilation and perfusion of the lung will affect this function considerably and the apparent DLco value does not truly represent the physical dimensions of the alveolo-capillary membrane.

JUSTIFICATION FOR THE STUDY

At present it is possible to measure pulmonary blood flow, parenchymal tissue volume, total diffusing capacity of the lung and membrane diffusing capacity by the gas chromatography technique[70] as described by Johnson et al and Lawson and Johnson. This method obviates the potential risk of cardiac catheterization and avoids any discomfort to the experimental subject.

This investigation attempts to evaluate the above mentioned variables in patients with bronchial asthma, as this information is

presently available only to a very limited extent. Also, by repeating these measurements following the administration of Adrenalin and Isoproterenol, two of the most commonly used bronchodilators, it is hoped to be able to further elucidate the site and mode of action of these drugs in bronchial asthma.

HYPOTHESIS

Colebatch[28] following induction of a stimulated asthmatic attack in cats and upon histological examination noted signs of gross pulmonary edema in two out of five cats. Earlier investigators noted that changes in pulmonary function, closely mimicking those found in bronchial asthma, can be produced solely on the basis of alteration of the pulmonary circulation.

Acetylcholine, Histamine, Bradykinin and 5 Hydroxytryptamine (Serotonin), substances that are currently suspected of being involved in the pathogenesis of bronchial asthma, are potent vasoactive substances. Therefore the possibility exists that part of alteration of pulmonary function in asthma may be explainable on the basis of changes in the pulmonary and, to a lesses extent, bronchial circulation.

The effects of Adrenaline and Isoproterenol on the diffusing capacity of the lung in asthmatics and particularly their effect on the membrance component of the diffusing capacity and capillary blood volume and capillary blood flow have not been adequately studied. This investigation attempts to determine the effect of these therapeutic agents on the above pulmonary parameters as well as their effects on pulmonary parenchymal tissue volume and forced expiratory volume at one second.

DEFINITION OF TERMS[9,50,98]

Diffusing capacity: the rate of gas transfer through a membrane in relation to a constant pressure difference across it. A simple physical concept that in biology is usually a complex measurement because of difficulty in accurate determination of the effective pressure difference.

Diffusing capacity of the lung for carbon monoxide (in milliliter of gas/minute/millimeter of mercury pressure difference): the capacity of the pulmonary membrane to transfer carbon monoxide from alveoli into the red blood cells.

Membrane diffusing capacity (in milliliters/minute/millimeter mercury pressure difference): a component of total diffusing capacity which includes every factor affecting carbon monoxide transfer other than pulmonary capillary blood volume (Vc) and the kinetic constant (θ). It thus includes both qualitative and quantitative aspects of the alveolar surface together with other additional factors.

Kinetic constant (θ) (in milliliters/minute/millimeter of mercury pressure difference): the rate of combination of carbon monoxide with red blood cells. It is affected by the alveolar oxygen tension simultaneously present.

Diffusing capacity components: components of total diffusing capacity (DLco) may be represented as follows:

$$\frac{1}{DLco} = \frac{1}{Dm} + \frac{1}{\theta\ Vc}$$

Pulmonary capillary blood volume (Vc): (in milliliters) - the volume of blood in the lung in contact with alveolar gas at any instant.

Pulmonary capillary blood flow (Qc): (in milliliters/minute) - the amount of blood flow through the pulmonary capillaries per minute.

Pulmonary tissue volume (Vt): (in milliliters) - the volume of the parenchyma of the lung.

Alveolar volume (VA) (in milliliters): total volume of air on the lungs from which diffusion occurs, this is the volume of air inspired added to the residual volume of the lung.

Anatomic dead space (in milliliters): the volume of non-gas-exchanging passages in the lung, normally comprising the upper airway and bronchial tree as far as the respiratory bronchioles.

Physiological dead space (in milliliters): a number (not a topographical volume) which by comparison with the anatomic dead space expresses the nonuniformity of ventilation perfusion ratios in the lungs.

Relative permeability of the red cell membrane (λ): the ratio of red blood cell membrane permeability to that of the interior of the corpuscle, the extremes of which are infinity, corresponding to an infinitely permeable membrane, (or no membrane at all) and 1.5, a lower limit of values actually found. Average value of red cell permeability: λ =2.5.

Carrier gas: the mobile phase in gas chromatography; the gas that is used for the movement of the sample through the column.

Chromatography: a physical method of separating a misture into its gas.

Detector: the element in the gas chromatograph which measures change in the composition of effluent from the column.

Peak: the recorded response of a differential detector to the presence of a sample component.

Retention time: the time taken for the gas mixture to traverse the column.

Thermal conductivity: heat conduction capacity of a gas. This varies with different gases, being high for helium and low for respiratory gases.

CHAPTER II

REVIEW OF THE LITERATURE

DIFFUSING CAPACITY OF THE LUNG

The diffusing capacity of the lung (DL) provides an index of the pulmonary capillary bed and pulmonary capillary membrane, as well as an estimate of the efficiency of this system in the exchange of the respiratory gases.

According to present theory[105], $\frac{1}{DL} = \frac{1}{Dm} + \frac{1}{\theta Vc}$

Where:

DL is the diffusing capacity of the lung, Dm is the diffusing capacity of the pulmonary membrane and θ Vc is the diffusing capacity of the red blood cells in the pulmonary capillary bed at any moment. All are expressed in milliliters per minute per millimeter of mercury pressure gradient. θ is the rate of gas uptake by one milliliter of normal whole blood per minute for one mm H_g pressure difference, and Vc is the average volume of blood in pulmonary capillary in milliliters.

Dm is dependent on: a) total surface area of the alveolar membrane

b) average thickness of the alveolar membrane

c) diffusion coefficient of the gas.

θ is determined by: a) the rate of gas uptake per red cell per millimeter of mercury pressure gradient.

b) concentration of red cells in pulmonary capillary blood.

Vc is a function of the capillary dimensions and is dependent on the average diameter and total length of the capillaries.

Correct DL is modified by the above mentioned factors, however experimentally determined diffusing capacity in addition is affected by non uniformity of ventilation and perfusion and finally by technical errors.

In the presence of ventilation perfusion imbalance, the true DL (the sum of individual DL's for each alveolus) can not be accurately determined with available techniques.

According to Roughton[105], gas exchange in the lungs occurs in three main steps: exchange within the alveolar gas, exchange across the pulmonary membrane, and finally diffusion and chemical combination of the gas with the hemoglobin inside the pulmonary capillary blood.

At least in normal subjects, the diffusion inside the gaseous parts of the smallest respiratory units is so rapid that no significant impediment to gas exchange appears to exist. Gas exchange across the pulmonary membrane constitutes one of the major limiting processes in pulmonary gas exchange.

Those gases which combine with blood elements can not do so instantateously; this would allow pressure gradients to develop within the blood itself. This produces an effective impedence to the further

uptake of the gas in the blood, and intracapillary resistance analogous to the diffusion resistance of the pulmonary capillary membrane. Certainly in the case of carbon monoxide, probably in that of oxygen, and possibly in that of carbon dioxide, under certain conditions, this intracapillary resistance may be as important as the diffusion resistance of the pulmonary capillary membrane.

The equation used for the calculation of the diffusing capacity of the lung for carbon monoxide was originally given by Krogh[68],

$$DL_{co} = \frac{VA(STPD)\ 60}{(PB-47)} \times \frac{1}{t} \quad \log_n \frac{(FA\ co\ 0)}{(FA\ co\ t)}$$

Where:

DLco: diffusing capacity of the lung for carbon monoxide in milliliters STPD/minute/mm Hg pressure gradient.

VA: alveolar volume in milliliters STPD

(PB-47): Barometric pressure less the pressure of water vapor in the alveolar volume

t: breath-holding time in seconds,

log n: natural logarithm

FAco 0: the initial concentration of carbon monoxide in the lung before diffusion occurs,

FA co t: the fractional concentration of carbon monoxide in the alveolar sample.

Factors modifying the diffusing capacity of the lung

Age: There is definite evidence of a fall in diffusing capacity with advancing age[21]. According to Burrows[21] the rate of drop for men and women is 0.238 and 0.117 milliliters per year respectively. Donevan et al[34] reported a significant drop in the pulmonary diffusing capacity with increasing age. They suggested that the observed decrease in DL may be explained by a diminution in cardiac output with advancing age.

Vital Statistics: A direct relationship between the body surface area and DLco has been reported. The following prediction formula has been introduced by Burrows: DL = 15.5 x B.S.A. - 4.6 Burrows[21] and McGrath[84] considering age and body size proposed the following prediction formulae for carbon monoxide diffusing capacity for men:

DL = 15.5 X B.S.A. - 0.238 age + 6.8 (Burrows)

DL = 24.246 X B.S.A. -0.289 age + 3.4 (McGrath)

The prediction formula, they proposed for women is: DL 15.5 X B.S.A. -0.117 age + 0.5. The average predicted Dlco values for healthy adult males by equations of Burrows, Ogilvie and McGrath were 23.3, 27.1 and 28.6 respectively.

Regression equations of diffusing capacity as a function of surface area, height and weight are as follows:

DL = Surface area (in square meters) X18.85 - 6.8

DL = Height (in inches) X0.874-31.6

DL = Weight (in pounds) X0.149+5.2

Correlation coefficients of diffusing capacity with surface area, height and weight are 0.81, 0.74 and 0.78 respectively (Ogilvie).

Body position: DLco measurements taken with the subjects in the supine position are approximately 15%-20% higher than those derived when subjects are sitting, and the latter values are 10%-15% higher than DLco's measure in standing position in the same individual[29].

Intra-thoracic pressure: Diffusing capacity is decreased with Valsalva manoeuver, this is partly due to increase in the intrathoracic pressure with consequent constriction of the great veins which results in decrease in venous return and cardiac output. It is for this reason that it is best that the inspiratory volume of the gas mixture taken into the lung for the measurement of diffusing capacity be approximately two hundred milliliters below the vital capacity.

Carbon monoxide back pressure: Diffusion of carbon monoxide across the pulmonary alveolo-capillary membrane will be impeded by plasma carbon monoxide back pressure. This error will be minimized by keeping the initial carbon monoxide concentration at fairly high levels. In extreme cases an eight per cent error could be generated by the operation of this factor.

Variation in the lung volume: Hamer[49] estimated the components of the pulmonary diffusing capacity at different lung volumes in seven normal and two patients with sarcoidosis. The membrane components of DL was shown to increase approximately in proportion to lung volume from a half to total lung capacity. The change was thought to be due to expansion of alveoli as the lung inflated. With the expansion of the lung from a half to three quarters of the lung volume, there is a decrease in

pulmonary capillary blood volume which conteracts the increase in membrane component of the diffusing capacity.

Krogh[68] believed that diffusing capacity is independent of pulmonary volume up to a level corresponding to mean capacity, however when the lung volume became larger DL increased in simple proportion to the alveolar volume.

Forster[39] estimated the relative changes in the pulmonary diffusing capacity with changes in the total lung capacity on two normal subjects by two independent methods. There was indication that DLco does not increase appreciably with increasing lung volume.

According to Miller et al[88], the membrane diffusing capacity increases as the lung volume expands from functional residual to total lung capacity and the increase is proportional to the estimated increase in alveolar surface area. This increase is noted both during rest and exercise.

According to McGrath, within one liter of maximal lung volume DLco is critically dependent on alveolar volume[84].

Ogilvie et al[94] measuring diffusing capacity in five subjects on whom alveolar volume was purposely kept low, and again when volume was high, found that when alveolar volume increased on the average by 56%, diffusing capacity increased by only 9%. Marshall on the other hand showed that when alveolar volume increased 56% the increase in DL was 24%. He also demonstrated that diffusing capacity, as measured by single breath

and steady state methods, was the same in normal subjects when allowance was made for the difference in the lung volume at which the measurement was made.

Breath-holding time: A standard breath-holding time is essential in the measurement of DL CO, since diffusing capacity become progressively lower as breath-holding time increases. This is most probably due to the uneven distribution of diffusing capacity throughout the lung[39]. Diffusing capacity will be underestimated if inspiratory time is prolonged; the reason for this is that the average time the CO molecules are in the lungs will be overestimated. Ten seconds has been chosen as the standard inspiratory time for single breath technique[85,92,94,102].

The portion of the expired alveolar gas sampled: in this regard the question arises whether the particular alveolar sample collected is representative of the whole lung in regard to diffusing capacity. There is evidence that the ratio DL/alveolar volume is not uniform throughout the lung. It is also known that the early portions of an expiration are derived from better ventilated alveoli than the later portions, so it might be expected that the different parts of the expired breath would come from varying diffusing capacity. Ogilvie[94], however, concludes that for clinical purposes the observed difference is insignificant, as, under grossly exaggerated conditions he showed an average change in DL of only 10 per cent.

Alveolar oxygen tension: Dl decreases proportionately as the alveolar oxygen tension is increased. This is due to competition of oxygen and carbon monoxide for pulmonary intra-capillary hemoglobin.

DL values while breathing 100 per cent oxygen may be as low as half of the values derived while breathing room air. Over a range of mean capillary O_2 tension from 40 to 200 mm. Hg the correct DL equals measured DL x (0.70 + 0.0027 mean capillary O_2 tension in mm Hg)[40].

Exercise: An increase in DL with exercise has been observed uniformly by all investigators beginning with Krogh. Data of Lewis et al confirm the increase in Vc in exercise previously observed by Roughton and Bates et al[7,8] and show that an increase in membrane component of the diffusing capacity also occurs[76].

Diffusing capacity increases during exercise owing both to an increase in the effective pulmonary capillary blood volume (Vc) and to an increase in the diffusing capacity of the alveolar capillary membrane (Dm). Vc may increase either because of distension of pre-existing patent capillaries or opening of new capillaries.

Assuming that the physical and chemical properties of the alveolar capillary membrane remain constant, surface area and thickness of the membrane are the important variables determining the membrane component of the diffusing capacity.

In the case of opeining of new capillaries with the same distribution of surface to volume ratio as those previously patent, membrane surface and capillary volume would increase proportionately and

Dm and Vc would show the same percentage of increase. However, if increase in Vc is primarily by the expansion of the pre-existing capillaries, volume change would be out of proportion to the surface area change and capillary volume would increase by a greater percentage than the Dm.

Data presented by Johnson[61] suggest that, during exercise, Vc increase by a greater percentage than Dm whereas Lewis et al using similar methods reported proportionately greater increase in Dm than Vc.

The character of plasma flow in the capillaries, whether predominantly laminar or turbulent, and extensive regional shifts in hematocrit caused by changes in the amount of plasma skimming, also may alter the ease of gas diffusion through plasma thereby changing Dm.

Physical training: The effects of physical training on the pulmonary diffusing capacity was studied by Reuschlein et al[103]. In spite of the fact that they did not exclude the occurrence in the athlete of high DL values from some inherent anatomic feature, their study did not support the concept that DL even when adjusted for changes in weight, is increased by training. This is, of course, in disagreement with the data of Bates and several other investigators claiming "supernormal" DL values in the athlete[8].

Pulmonary-vascular pressures: The changes in pulmonary diffusing capacity with change in pulmonary vascular pressures were reported separately by Lawson et al[71] and Brugess and colleagues[20]. The data of the latter indicate that pulmonary inflow pressure has a significant influence on

pulmonary capillary blood volume, and a directional change in DL with alteration of the pulmonary artery pressure. They suggest that increasing pulmonary pressure may result in recruitment of a large number of pulmonary capillaries which are previously underperfused. They propose that arterial segment of the pulmonary circulation may act normally as a system with significant critical opening pressure. Their conclusions differ from those of Lawson, who, using cats demonstrated that changes in inflow pressure did not affect diffusing capacity significantly.

In critique of the breath holding experiment it is stated that respiratory gymnastics involved in this technique may produce alterations in pulmonary blood flow resulting in secondary changes in DL. Although the absolute value of diffusing capacity may be incorrect, comparative measurements should be correct as should the relation of pulmonary membrane diffusing capacity to pulmonary capillary blood volume[76].

Pulmonary DL & Capillary Blood Flow: Johnson et al noted a positive correlation between DL and it components Dm and Vc, and the pulmonary capillary blood flow ($r = 0.92$, 0.71 and 0.92 respectively)[61]. On the other hand, in experiments of Lawson et al there was no significant change in DLCO with increase of pulmonary capillary blood flow about threefold. This was in agreement with the data of Ross and co-workers who showed that an acute increase in cardiac output in resting man produced by infusing epinephrine or norepinephrine did not alter DLco.

Measurement of diffusing capacity and cardiac output in resting hyperthyroid patients after therapy revealed a fall in cardiac output as is expected but no change in DLco was detected[61]. The most probable cause of lack of increase in diffusing capacity in spite of high pulmonary capillary blood flow seems to be a decrease in the capillary transit time secondary to higher velocity of blood.

Caldwell and co-workers reported a marked fall in diffusing capacity following prolonged (more than 30 hours) of breathing oxygen. Analysis of their results indicated that the diminution in the DL resulted primarily from a decrease in the membrane component with no consistent change in pulmonary capillary blood volume. The effect of oxygen breathing of shorter duration on the diffusing capacity has been reported to be variable[23].

Diurnal variation: Diurnal variation in diffusing capacity for carbon monoxide was measured by Cinkotai,[26] in twenty four normal subjects at two hour intervals. He noted a progressive fall throughout the day at a rate of 1.2%/hour between 9:30 A.M. and 5:30 P.M., and at 2.2%/hour between 5:30 P.M. and 9:30 P.M.

Significant differences between Dlco values of the right and left lung were demonstrated by Glauser[45] using eight healthy adult male dogs.

Non uniformity of DL: Hatzfeld et al[51] emphasized the effect of inhomogeneity of the lungs on the diffusing capacity, a finding which was pointed out earlier by Forster and Fowler[39] and Keukniet and Visser[67]. Hatzfeld

computed the true diffusing capacity, on the assumption that it is distributed (a) in proportion to the lung volume and (b) in proportion to blood flow. The computed diffusing capacity was about twice the measured values in most of their patients who had severe obstructive lung disease. He postulated that decreased measured values may be due to uneven distribution of the diffusing capacity and of ventilation in the lungs, and that they are compatible with a normal total diffusing capacity. So, in patients with non uniformity of ventilation and perfusion, diffusing capacity will not give a correct indication of the existence of diffusion impairment. Data of Burrows et al[22] confirm previous reports of non uniformity of diffusing capacity and alveolar volume DL/VA in normal subjects and pulmonary patients.

Although the exact cause of unevenness of DL in normal subjects is not known, undoubtedly poor perfusion of the upper portions of the lung due to gravity plays a part. Their theoretical calculations in five normal individuals indicate that the lung behaves as though 6 to 18 per cent of its volume contains 12 to 46 per cent of its diffusing capacity withDL/VA variations ranging from two to fourfold. They emphasize the possible errors in total DL when there is marked non uniformity of diffusion, and seriously question the meaning of a conventionally determined DL under these conditions, since, according to them, it is impossible to know whether one is obtaining an index of the best or the poorest diffusing region in an individual patient. Apparent changes in DL with therapy or with altered physiological state could represent only a variation in emphasis of different lung regions rather than a true

alteration in total pulmonary diffusing capacity.

Since DL/VA variation in normals is at a minimum at the resting lung volume close to the normal functional residual capacity it has been suggested to perform routine breath holding tests as a lung volume close to the normal functional residual capacity.[90]

PULMONARY DIFFUSING CAPACITY IN BRONCHIAL ASTHMA

Pecora[97] described the pulmonary diffusing capacity in twelve children with intractable asthma and hyperinflated lungs, and five children with intractable asthma and irregularly occuring hyperinflation. Both these groups had diffusing capacities slightly lower than the normal range.

The same authors later described different findings in another group of asthmatic children. They found increased pulmonary diffusing capacity and markedly increased membrane diffusing capacity in ten asthmatic children with overinflation, another ten asthmatic children without overinflation of the lungs had DL, Dm and capillary blood volumes (Vc), as predicted.[96]

Pulmonary diffusing capacity was measured by Miyamoto[91] in thirty patients with ordinary asthma, and eight patients with Yokohama asthma. The diffusing capacity in both groups was found to be in the range of normal subjects.

Bates[9] measured the percentage uptake of carbon monoxide in thirteen young asthmatics aged 12 to 19 years and found an abnormally low figure in only one.

Ogilvie et al[94] mention one asthmatic patient whose diffusing capacity was normal.

Effects of Isoprenaline and prednisone on the diffusing capacity in 47 patients with asthma and emphysema were studied by Lorriman.[79] In this study even when there was a considerable increase in forced vital capacity at one second (FEV) there was no increase in DLco. In patients who received prednisone and responded with a considerable increase in FEV 1, a pronounced increase in diffusing capacity did occur. Knudson[66] observed the effect of Isoproterenol on ventilation perfusion ratios in four symptomatic asthmatics and two normal subjects. He noted a fall in DLco in asthmatics after inhalation of Isoproterenol, a potent broncho-dilator, but none in normal subjects. He suggested that the administration of Isoproterenol aerosol to asthmatics increased the ventilation of the already well ventilated portions of the lung to the detriment of the poorly ventilated portion, thus further increasing the uneveness of distribution of ventilation perfusion ratios throughout the lung.

Kanagami et al[64] studied pulmonary diffusing capacity in five patients with bronchial asthma and found mean DLco of 33.14 cc/minute/mmHg (132% of predicted). They interpreted their finding as due to over-distension of the lung. Dlco increased proportionally with exercise which

meant increase of pulmonary capillary bed and blood flow. They concluded that patients with bronchial asthma have a considerable reserve in their pulmonary capillary bed.

PULMONARY PARENCHYMAL TISSUE VOLUME

Cander and Forster,[24] in 1959, used inert soluble gases such as nitrous oxide and acetylene to determine the pulmonary capillary blood flow and pulmonary tissue volume.

During breath-holding following a single deep inspiration of a gas mixture containing N20 and C2H2, they noted a paid initial fall (less than 1.5 second) in relative alveolar concentration of N20 and C2H2, followed by a subsequent more gradual decrease in the alveolar concentration. The initial rapid fall resulted from the solution of gases in the pulmonary parenchymal tissue volume, and the more gradual decline in the concentration was thought to be due to solution in the pulmonary capillary blood.

The magnitude of the capillary blood flow in contact with the alveolar gas determined the rate of fall of the acetylene.

The accepted equation for tissue volume is:

$$Vt = \frac{VA}{\alpha t}\left[\frac{100}{\text{C2H2 intercept at t.0 in\%}} - 1\right] \times \frac{760}{PB - 47}$$

Where:

Vt: pulmonary parenchymal tissue volume in milliliters

VA: alveolar volume in milliliters

Intercept (C2H2) at t.0 in%: the intercept of the regression line drawn on asemilogarithmic paper, with the logarithm of the alveolar concentration of C2H2 divided by the initial concentration of C2H2 before dilution, on the Y axis and the breath-holding time on the X axis, expressed as a percentage.

(PB-47): barometric pressure less the water vapor partial pressure at body temperature in millimeter of mercury.

αt: Bunsen solubility coefficient of acetylene in pulmonary parenchymal tissue, (0.768 milliliter/milliliter tissue/atmosphere at 37 C.)

In order to calculate tissue volume and capillary blood flow the disappearance curve of acetylene must first be established and it is essential that there should be at least four repeats of the test. The disappearance ratio is ploted for each breath-holding time on the "X" axis, and the logarithm of FA C2H2t/FAC2H20 on the "Y" axis.

PULMONARY CAPILLARY BLOOD FLOW

The equation for the measurement of the pulmonary capillary blood flow as modified by Johnson et al is as follows:

$$Qc = \frac{VA \times 760 \times 60}{\alpha B \left(\frac{VA}{VA\ t.Vt}\right)(PB\ 47)X\ t} \times \log n \frac{VA}{VA + \alpha t.Vt} X \frac{FAC2H2.0}{FAC2H2.t}$$

Where:

Qc: pulmonary capillary blood flow in milliliters/minute

VA: alveolar volume (STPD) in milliliters

$\alpha\beta$: Bunsen solubility coefficient of acetylene in blood -0.740 milliliters of gas/milliliter of blood/atmosphere at 37 C.

Vt: tissue volume of lung in milliliters

t: breath-holding time as determined by Jones and Meade[63] in seconds.

(PB 47): barometric pressure less water vapor partial pressure at 37 C. in mmHg.

log n: natural logarithm

FAC2H2.0: fractional concentration of acetylene in the lung before any dilution of diffusion has occured.

FAC2H2.t: fractional concentration of acetylene in the alveolar sample.

Pulmonary capillary blood flow (Qc) may also be estimated from the slope & intercept of the linear fall of Ln(FAC2H2.t/FAC2H2.0) with time[61] as below.

$$Qc = \frac{VA \times 760 \times 60}{\alpha\beta \left(\frac{VA}{VA + \alpha t . Vt}\right) (PB-47)} \times \frac{\log n \, (FAC2H2.t/FAC2H2.0}{t}$$

or

$$Qc = \frac{VA \times 760 \times 60}{\alpha\beta \left(\frac{VA}{VA + \alpha t . Vt}\right) (PB-47)} \times \beta \text{ slope of Acetylene disappearance}$$

The latter equation has been used to calculate the pulmonary capillary blood flow.

In the hands of most investigators the use of inert soluble gases for measuring pulmonary blood flow has given results in resting subjects about 25% lower than those obtained by the use of direct Fick principle.

Some of the recognized sources of error in measurement of pulmonary blood flow by the acetylene method are as follow:

a) any recirculation of acetylene into the lungs after a long breath-holding time. This may, however, be recognized as a change in the slope of the disappearance curve, and be avoided.

b) failure to consider lung tissue as a reservoir for dissolved acetylene.

c) uncertainty about alveolar volume from which the acetylene is absorbed. Alveolar volume is overestimated by the amount of anatomic dead space.

d) uncertainty of the Bunsen solubility coefficient of acetylene in blood. The Bunsen solubility coefficient of acetylene in blood as determined by Grollman and used by Johnson[68] is 0.740 which is approximately six per cent higher than that determined by Chapman and his associates, the latter appears to be more correct.

e) alteration of blood flow by the respiratory manoeuvers.

f) non uniformity of ventilation and perfusion of the lung.

g) shunting of blood around ventilated lung capillaries.

PULMONARY CIRCULATION IN BRONCHIAL ASTHMA

The changes in the pulmonary circulation during attacks of bronchial asthma have not been well studied.

Observation of increase in systolic and diastolic pressure in pulmonary artery during catheterization in a patient with bronchial asthma who developed spontaneous attack prompted Zimmerman[123] to study the dynamics of the pulmonary circulation in bronchial asthma. His ten patients either had a spontaneous attack of asthma or one that was induced by subcutaneous administration of 5-10 mg of Mecholyl. Zimmerman noted an increase in pulmonary artery pressure in all persons with moderate to severe bronchial asthma. The effects of aminophyllin and adrenalin were also observed in this group of patients during an asthmatic attack. Adrenalin relieved the bronchial asthma, but maintained pulmonary artery pressure at the asthmatic level because of constriction of pulmonary arterioles. Aminophyllin relieved the bronchial asthma, but caused dilatation of the pulmonary arterioles, thus lowering pulmonary artery pressure below normal. The average drop in systolic and diastolic pressures was 35 and 55% respectively.

Helander et al[52] studied pulmonary circulation in thirty-four male patients who suffered with bronchial asthma, but who were at that time as free from symptoms as possible. The patients were divided into three groups according to the clinical severity of their asthma. The investigators noted normal pulmonary vascular resistance, however the resistance increased significantly with the severity of the disease.

The effects of hypercapneic and hyperoxic breathing on the pulmonary circulation were studied by Irnell[59] in patients with uncomplicated bronchial asthma during symptom free intervals. During inspiration of 5% carbon dioxide in air significant rise in pulmonary artery pressure was noted.

Storsein et al[115] studied the ventilatory and circulatory effects of theophyllin ethylenediamine in twenty-one patients with various cardio-pulmonary diseases. They noted a pronounced fall in pulmonary artery pressure as well as a marked fall in the pulmonary vascular resistance. This indicated that pressure drop was mediated through a direct dilating effect of theophylline on the pulmonary arterioles. In three of their asthmatic patients in this group, the mean pulmonary artery pressure was 11 and 9 millimeter mercury which, following intravenous administration of theophylline, dropped to 5.5, 6.5 and 6 mmHg respectively.

In regard to the influence of alveolar pressure on pulmonary vascular resistance, it is stated that whenever alveolar pressure is higher than left atrial pressure, the blood flow through the pulmonary circulation will be determined by the pressure gradient between the pulmonary artery and the alveoli. This phenomenon, which has been referred to as the sluice mechanism or the vascular waterfall, could easily come into play in the case of bronchial asthma where an increased alveolar pressure is necessary for expiration.

The fact that inhalation of histamine will elicit an attack in an asthmatic subject is well known. It is also known that an injection of histamine decreases pulmonary artery pressure and pulmonary vascular resistance in non-asthmatic subjects.

In one asthmatic group in whom an attack was provoked by inhalation of histamine an increase in pulmonary artery pressure and vascular resistance was noted. This is an effect which can not be explained by direct action of histamine on the blood vessels. In four patients in whom histamine was administered intravenouly no asthma attack was induced and a decrease in pulmonary vascular resistance below the value at rest was noted.

CHAPTER III

APPARATUS, MATERIALS AND METHODS

FIGURE 1
APPARATUS FOR USE WITH THE SINGLE BREATH TECHNIQUE

APPARATUS FOR THE SINGLE BREATH STUDY

The component parts of the apparatus consist of:

1. respiratory circuit
2. electrical switches, control unit and automatic syringe sampler

The respiratory circuit has the following components:

a. Donald Christie bag-in-a-box

b. twelve liter wet spirometer

c. Hans-Rudolf valve and connecting tubes

The polyvinyl meterological balloon inside a twelve liter glass bottle is connected to the Hans-Rudolf valve through the vertical arm of a T-union and a series of polyvinyl and stainless steel tubes. One of the intermediary tubes between the balloon and the Hans-Rudolf valve contains a one way valve which prevents blowing of expirate back into the balloon.

Excluding the mouthpiece, the Hans-Rudolf valve has four outlets which will be identified as follows: port #1, supplies normal air direct from the atmosphere, port #2 supplies the special inspiratory gas mixture, port #3, leads to expiration collection system, port #4, this port is connected to the atmospheric air.

These ports are arranged in such a way that with a clockwise turn of the control tap the subject may be switched directly from port #1 to port #2, port #3 and port #4 in sequence.

The inspiratory gas mixture is inhaled by the subject from the meteorological balloon when the mouth piece of the four way valve is connected to port #2. Port #3 of the Hans-Rudolf has connection with the inside of the glass bottle through a stainless steel and a flexible plastic tube which itself is connected to one of the two ends of the horizontal arm of the second T-union. The other end of the horizontal arm of the stainless steel T-union via another flexible plastic tube is connected to the 13 1/2 liter wet spirometer.

In this way inspiratory volume change may be recorded on spirometer recording paper, because a volume drop in the balloon due to inspiration is balanced by a drop in the volume of the spirometer. Expired volume may be directly recorded.

The second outlet of the spirometer is fitted with a detachable stopper so that following each trial the expiration system may be flushed out.

Because of the reactivity of acetylene with brass and copper all metal connections should be made of stainless steel. All tubing should be polyvinyl plastic material as acetylene diffuses rapidly into rubber and after a certain period the rubber becomes oversaturated and

releases acetylene back into the system.

A simple electrical switch is fitted on a quarter inch square section rod which itself is attached to the body of the spirometer. The switch can be moved up and down the rod and may be tightened to remain in any required position. The switch is designed so that only downward movement of the striker arm attached to the pen support of the recorder would allow contact for sufficient time to complete an electrical circuit. The signal from the switch passes into a control unit which enables the operator to select the syringe that is to be used for collection of the sample. Following the interpretation and appropriate orientation of the electrical signal, the catch that holds the respective syringe will be released, a spring automatically pulls back the stopper of the syringe and a fifty milliliter sample of the expiratory gas will be collected. Altogether three syringes are fitted to the sampler unit, so that three samples at different points during expiration may be obtained. For normal use, however, the control unit is simplified to operate only one syringe during a trial and the automatic sampler is fitted with only one syringe.

SPECIAL INSPIRATORY GAS MIXTURE

Gas of the following composition is used for the measurement of the total lung diffusing capacity as well as pulmonary capillary blood flow.

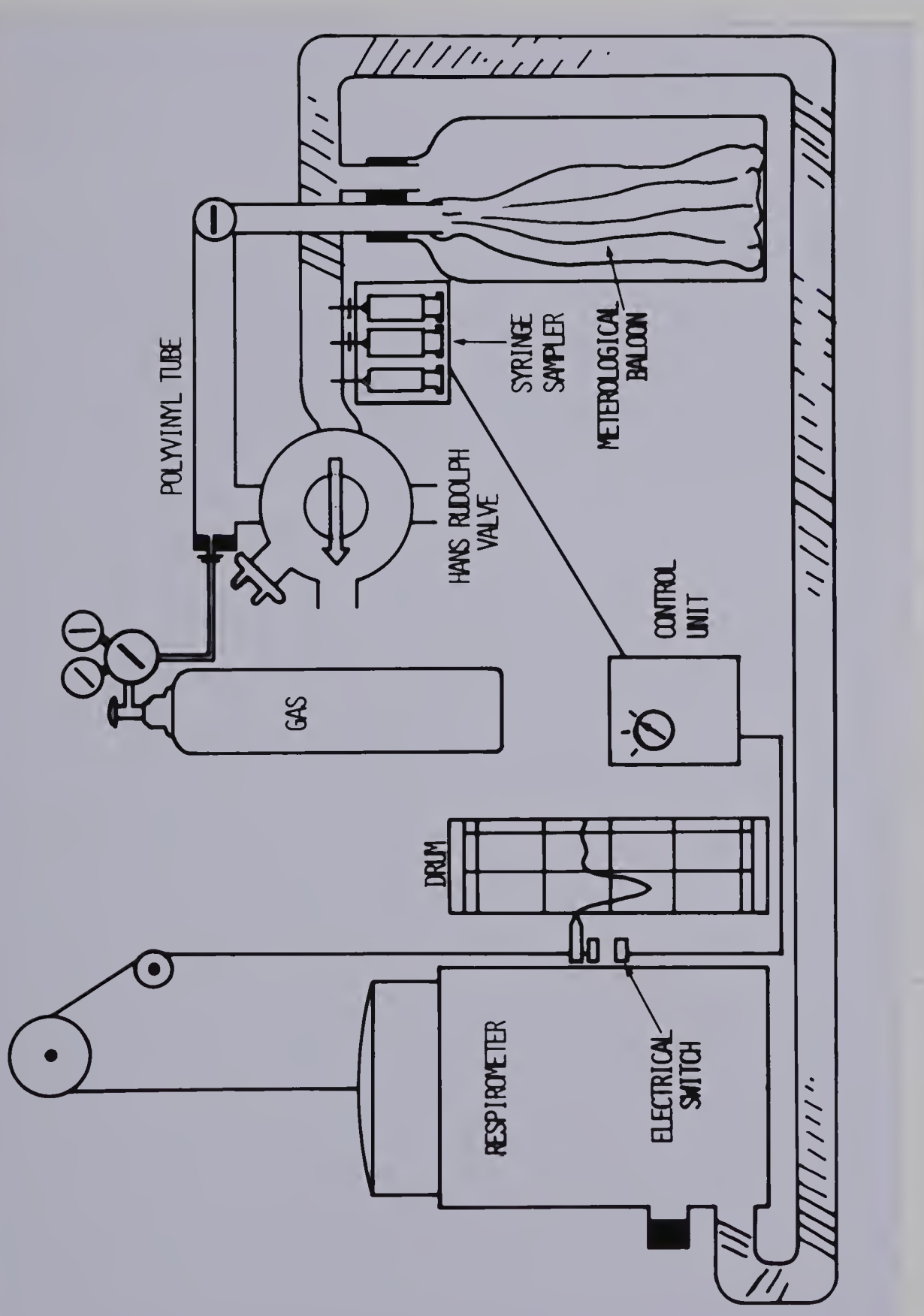

FIGURE 2
SCHEMATIC DIAGRAM OF APPARATUS FOR USE WITH THE SINGLE BREATH TECHNIQUE

GASES	CONCENTRATION
NEON (Ne)	0.350%
OXYGEN (O2)	20% approx.
NITROGEN (N2)	79% approx.
CARBON MONOXIDE (CO)	0.370%
ACETYLENE (C2H2)	0.454%

Another gas mixture of the following composition which supplies approximately ninety-five per cent oxygen is used to determine the diffusing capacity at high alveolar oxygen tension.

GASES	CONCENTRATION
NEON (Ne)	0.40%
OXYGEN (O2)	95% approx.
NITROGEN (N2)	4%
CARBON MONOXIDE (CO)	0.60%

This gas mixture does not contain acetylene, the reason being that mixture of acetylene and high concentrations of oxygen is potentially combustible. Because of absence of acetylene the measurement of pulmonary parenchymal tissue volume and pulmonary capillary blood flow, in trials in which this gas mixture is used can not be made.

A small cylinder of reference gas is used for the calibration of the other cylinders as well as adjustment of the ranges of the gas chromatograph. The composition of the reference gas is guaranteed and is accurated to the second decimal.

MATERIALS AND METHODS

Five normal volunteers and twenty patients with bronchial asthma serve as subjects for this experiment. The normal volunteers consist primarily of hospital staff personnel without known personal or family history of asthma. The twenty asthmatic patients are selected from the in-patient and out-patient services of the University of Alberta Hospital.

An attempt was made to select young patients with history of well documented bronchial asthma and without associated significant disease.

The subject is allowed to rest quietly for several minutes after arriving in the laboratory, during which time the procedure is explained and demonstrated to him. The meteorological balloon is evacuated, filled with the inspiratory gas mixture, flushed through and is refilled. A sample is drawn from the bag and is fed to the gas chromatograph. The subject is then fitted with a nose clip and is brought to the mouthpiece on the four-way valve and is allowed to breathe through port #3 into the expiration circuit. The subject is instructed to exhale fully following a deep inhalation so that vital

capacity can be recorded.

This procedure is repeated for an average of three to four times for the calculation of the mean effective vital capacity.

The subject is instructed to repeat the same procedure, but to inhale as much as possible without straining; this value usually is 200-300 milliliters less than the previously measured vital capacity.

While the subject is allowed to rest, the electrical switch is positioned on its shaft, so that, if the subject continues to make inspiration to a reproducible inspired volume, the striker arm will activate the switch only on expiration and after 1200 milliliters (equivalent amount needed to wash out dead space), has been exhaled.

The subject is then readied for the series of trials. He is fitted with a nose clip and a mouthpiece; the tap on the Hans-Rudolf valve is turned so that the subject breathes room air through port #1. On instruction, the subject completely exhales through #1 and signals by snapping his fingers when he can exhale no more air. At this signal the control tap is turned to port #2 and the subject is told to inhale as rapidly as possible. Immediately following the completion of inspiration the tap is turned to a neutral position between ports #2 and #3 so that no gas exchange can occur.

At the end of the desired breath holding time which may vary between four and twelve seconds the tap is turned to port #3 and the

subject is instructed to exhale rapidly. After the sample has been collected, the control tap is turned to port #4 and the subject is allowed to remove the mouthpiece.

The collection syringe containing the alveolar sample should be removed from the apparatus immediately and flushed through the chromatograph. After a one or two second delay which is allowed for pressure equalization the sample injector is activated and the sample is taken up for analysis.

A ten to fifteen minute rest period should be allowed between the trials. The length of this period may coincide with the analysis time of the chromatograph. The rest period is usually longer than the two to four minutes which is required for complete elimination of the foreign gases from the subject's lung. For this reason no capillary carbon monoxide back pressure is determined in this experiment. Following four trials with inspiratory gas mixture containing approximately 20 per cent oxygen, the patient breathes approximately 95 per cent oxygen for a period of twenty minutes, during this time the patient breathes from a bag which is connected to the 95 per cent oxygen tank in one end and the Hans-Rudolf valve in another. Adequate supply of oxygen, in the range of 15 liters per minute is provided throughout this phase. This period of breathing 95% oxygen will

provide an alveolar oxygen tension arount 600 mm Hg. At the end of this period of time, two further trials are made and the patient is maintained on high percentage of oxygen. Meanwhile, further low and high oxygen samples are obtained from the meteorological balloon and fed to the gas chromatograph and are used as controls.

The patient is given fifteen inhalations of 1/200 solution of Isoproterenol which is nebulized by the oxygen, immediately after the patient is connected to the high oxygen supply as was described earlier; two further single breath tests are performed and the patient is taken off from the apparatus. The early performance of high oxygen trials following administration of Isoproterenol is technically simpler, is less time consuming and is easier for the patient.

The sensitivity of the gas chromatograph detector which had been decreased during high oxygen testing is returned back to the pre-arranged levels. This is also true of the digital programmer which has to be changed to the previously determined points.

Following this necessary manoeuvering of these units, and after 20 to 30 minutes from the time of previous testing, the final four trials with low percentage of inspiratory oxygen concentration are done. The minimum length of time for the performance of the two sets of tests each consisting of six trials is three hours.

The final set of trials following the administration of 1/100 solution of Adrenaline or Isoproterenol is performed in the afternoon; hence assuring a minimum time interval of four hours between inhalation of Isoproterenol and Adrenaline. The time interval between inhalation of the medication and the beginning of each set of trials is approximately twenty minutes. This interval of time is compatible with the data of Mushin[93] which reveal a maximum bronchodilator effect following inhalation of Isoproterenol in approximately 30 minutes.

Knowing the DLco values for low and high alveolar oxygen tension the equation $\frac{1}{DL} = \frac{1}{Dm} + \frac{1}{\theta Vc}$ will be solved graphically for membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc). One of the components of θ, lambda which is the ratio of permeability of the red cell membrane to that of the interior of red cell has been found by Foughton and Forster to have a wide range of uncertainty (between 1.5 and infinity). Lambda of 2.5 is considered to be the most accepted value and is the assumed value in this study.

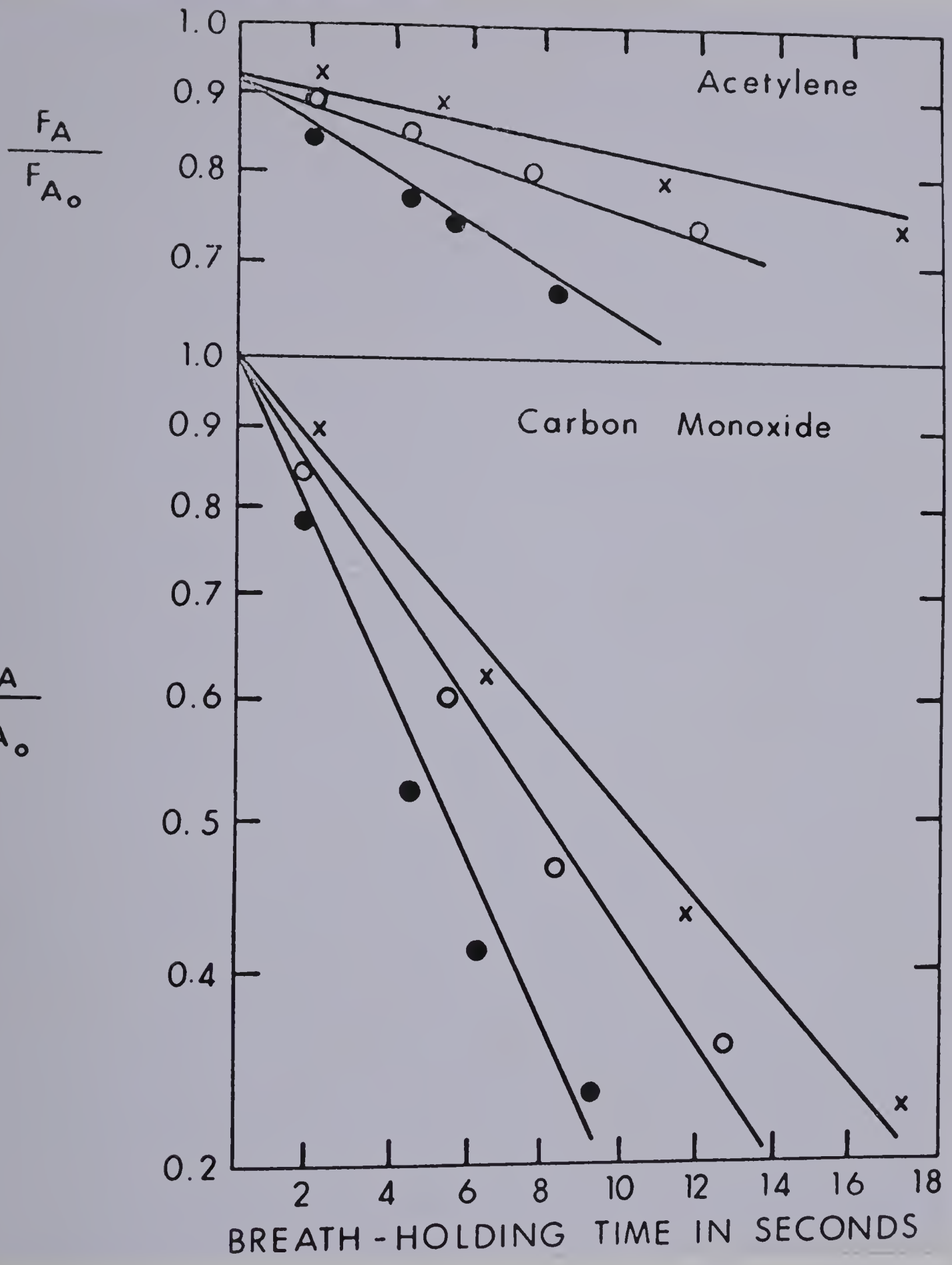

FIGURE 3

SIMULTANEOUS DISAPPEARANCE OF ALVEOLAR ACETYLENE AND CARBON MONOXIDE DURING BREATH HOLDING. MEASUREMENTS WERE MADE DURING A VALSALVA MANOEUVER (X), DURING REST (O) AND AT 5 MPH ON A 4 DEGREE GRADE (•)
From Johnson, et al

SELECTED CARDIOVASCULAR AND PULMONARY EFFECTS OF ADRENALINE (EPINEPHRINE) AND ISOPROTERENOL:[5,6,46]

In general, responses to epinephrine resemble the effects of stimulation of adrenergic nerves. Particularly prominent among the actions of epinephrine are those on the heart and the vascular and other smooth muscles. The effects of epinephrine, as generally known, are functions of the dose and method of administration.

Because of epinephrine's positive chronotropic and inotropic effects, the heart rate and stroke volume are both increased. The augmented venous return also contributes to the observed increase in the cardiac output.

Myocardial oxygen consumption is markedly increased, and the increase is out of proportion to the increase in cardiac output; consequently, cardiac efficiency is lessened. In accelerating the heart within physiological range, epinephrine shortens systole more than diastole so that the duration of diastole per minute is increased.

The chief vascular action of epinephrine is exerted on the smaller arterioles and pre-capillary sphincters, although veins and arteries also respond to the drug.

Intravenous infusion of 0.1 to 0.4 micrograms of the drug results in different reactions in various vascular beds. By the action of the drug on alpha receptors, the blood vessels to skin, kidney and mucosa are constricted whereas the vessels to skeletal muscles are dilated

by the action on their beta receptors.

Diastolic arterial blood pressure will be determined by the balance between the dilator and constrictor effects on different vascular beds and may variably be unchanged, decreased or increased. Because of the primary cardiac stimulant effect of the drug, systolic blood pressure will be moderately increased.

Arterial and venous pulmonary pressures are raised after the administration of epinephrine. Although direct pulmonary vasoconstriction can be shown under suitable conditions, the increase in pulmonary pressure in man is predominantly, if not entirely secondary to an increase, in left atrial pressure[46]. Undoubtedly, shift of blood from systemic to the pulmonary circulation plays an important role in the increase in pulmonary pressure.

Epinephrine has a powerful bronchodilator effect, most evident when the bronchial muscle is contracted due to disease as in asthma, or to drugs such as Histamine.

Epinephrine alters respiration by its alpha stimulant activity in both normal and asthmatic subjects. It increases vital capacity by relieving congestion of the bronchial mucosa, and, when its action is limited as much as possible to the pulmonary vascular bed through administration as an aerosol, by constricting pulmonary vessels. Because of its bronchodilator and local vasoconstriction effects following inhalation, the timed vital capacity would increase.

Intramuscular or intravenous injection usually causes a rise in pulmonary artery pressure amounting to 25 to 75 per cent in normal as well as asthmatic patients. Increase in pulmonary artery pressure has also been reported following inhalation of epinephrine aerosol by normal subjects[5].

Horisberger and Rodbard[55] have shown the difference between intravenous and bronchial arterial injection; the former causes a rise in bronchial arterial flow associated with systemic pressor response whereas injection into the bronchial artery causes a reduction inflow, indicatingavasoconstriction.

Isoproterenol is the most active of the sympathomimetic amines that ace almost exclusively on beta receptors. It has no proven action on alpha receptors. Intravenous administration of Isoproterenol raises cardiac output by the positive Inotropic and chronotropic actions combined with an increase in the venous return to the heart. With usual doses of Isoproterenol in man, the increase in cardiac output is generally enough to maintain or raise the systolic pressure, although the mean pressure is reduced.

The drug relaxes almost all types of smooth muscles when their tone is high. It is most pronounced on bronchial smooth muscle. It prevents or relieves bronchoconstriction due to drugs or bronchial asthma in man. Air way resistance will decrease and vital capacity will increase.

The results derived from the intact dog have been variable in terms of the relative importance of the pulmonary vasodilatation and the well known cardiac stimulant action of Isoproterenol. The experiments in man have consistently shown that the drug causes pulmonary vasodilatation[5]. Because of cardiac stimulant effect and decrease in pulmonary vascular resistance resulting from vasodilation the pulmonary blood flow will be increased.

Infusion of Isoproterenol into the pulmonary artery in patients with pulmonary hypertension and inhalation of the drug in patients with bronchitis have been associated with a fall of pulmonary artery pressure.[15]

CHAPTER IV

RESULTS AND TABLES

RESULTS

The results are shown in tables I through VIII. Group 1 represents our five normals. Group II includes the twenty-two asthmatic patients. Those patients who, following the control trials, received Isoproterenol first and Adrenaline later are grouped under IIA. The remaining ten patients in whom Adrenaline was used prior to the administration of Isoproterenol form group IIB . In table I are shown the physical characteristics of subjects in three different groups. Our normals were all males and varied in age between 19 and 42 years with mean age of 30.8 years. In group II A, there was one female and the mean age in this group was 50 years. There were three females in group IIB and the average age was 40.1 years.

Tables II, III and IV represent pulmonary diffusing capacity (DL), membrane diffusing capacity (DM) and capillary blood volume (Vc) of group I, IIA and IIB respectively. The upper row in the DL column shows the diffusing capacity when low (20.4%) oxygen was given and the lower row represents DL values when high (95%) oxygen was administered.

Means and the standard deviations are displayed in the two bottom rows in each column. We did not have the opportunity to study subjects F.R. and S.S. after adreanline.In group IIA following Adrenaline we had two values of Dm below 20 and one above 165 that we did not accept

and consequently did not include in the determination of the mean and the standard deviation. In group IIB five falues of Dm all below 270 but above 165 were also not accepted. In group IIA subject R.Y. had three determinations of capillary blood volumes the values of which were below 30 and ,thus, were excluded from our results.

Table .V shows vital capacity, FEV1 (a forced expiratory volume at one second), pulmonary parenchymal tissue volume (Vt), and pulmonary capillary blood flow (Qc) in group 1. The same parameters for group IIA and IIB are displayed in table VL. Qc values less than 1500 milliliters and above 10 litres have been excluded from the results. It is to be noted that our assumed vital capacity and forced expiratory volumes do not represent the true value of these parameters. When performing the test we instructed our patients to inhale deeply but also rapidly, the reason for the rapidity of the manoeuver was to obviate prolongation of the inspiratory time which could have distorted the DL values. This emphasis on fast inhalation during the performance of the test in our asthmatics who have pathologically increased air way resistance has undoubtedly contributed to the underestimation of the effect of bronchodilator.

The forced expiratory volumes have also been underestimated. In actual performance of the test our subjects following inspiration had to hold their breath prior to exhalation. The breath holding time was variable and ranged between three to thirteen seconds. This length of breath holding is unphysiological and inevitably distorts the spirographic tracings. The element of fatigue occuring during late morning and early afternoon testing at which time we performed our post medication trials has contributed to the further underestimation of the values of the so-called "FEV_1", following the bronchodilators.

In table VII is shown the means and the standard deviations of all the variables prior to and following Adrenaline and Isoproterenol in normals (group 1) and in asthmatics (group II).

Table VIII represents the values of the same variables in normals and in groups IIA and IIB. In DLco sections of table VII and VIII, the two values in the upper row show the means and the standard deviations of diffusing capacity at low oxygen tension. The values in the lower rows are representative of the same statistical variables at high oxygen tension.

TABLE I

PHYSICAL CHARACTERISTICS DATA

GROUP I SUBJECT	SEX	AGE Yrs.	HEIGHT Inches	WEIGHT Pounds	BODY SURFACE AREA
A.R.E.	M	29	71	145	1.84
G.C.	M	22	72	170	1.99
L.C.	M	42	74	187	2.11
T.S.	M	42	68	170	1.91
R.A.	M	19	75	155	1.97
MEAN	-	30.8	72	165.4	1.96
GROUP IIA					
P.S.	M	57	72	242	2.31
F.C.	M	42	69	172	1.94
J.R.	M	64	70	118	1.67
M.L.	M	52	70	167	1.93
P.P.	M	41	68	175	1.93
E.B.	M	42	68	170	1.91
R.Y.	M	72	66	154	1.79
F.R.	M	50	73	172	2.02
S.S.	M	53	65	195	1.96
G.V.	M	55	71	186	2.04
L.D.	M	21	68	142	1.77
A.R.	F	51	62	113	1.50
MEAN	-	50.0	68.5	167.2	1.89

TABLE I
(continued)

GROUP IIB

SUBJECT	SEX	AGE Yrs.	HEIGHT Inches	WEIGHT Pounds	BODY SURFACE AREA
B.V.	M	54	66	158	1.81
E.B.	M	63	66	168	1.86
R.B.	F	43	60	107	1.43
H.M.	M	40	66	132	1.68
E.D.	F	29	63	129	1.61
D.T.	M	49	71	187	2.05
N.O.	M	44	71	151	1.87
D.E.	M	34	72	200	2.13
B.B.	F	21	63	100	1.44
R.R.	M	24	65	126	1.63
MEAN	-	40.1	66.3	145.8	1.75

TABLE II

DIFFUSING CAPACITY (DL), MEMBRANE DIFFUSING CAPACITY (Dm), AND PULMONARY BLOOD VOLUME - GROUP I

	DL			Dm			Capillary Volume (Vc)		
SUB-JECT	CON-TROL	ADREN-ALINE	ISU-PREL	CON-TROL	ADREN-ALINE	ISU-PREL	CON-TROL	ADREN-ALINE	ISU-PREL
A.R.E.	36 18.2	35.6 15.6	33.0 13.9	71.5	91.8	97.5	100.7	80.4	68.4
G.C.	43.4 22.0	43.9 22.5	42.9 20.0	81.9	81.9	119.3	125.8	128.4	86.2
L.C.	28.1 15.1	26.7 16.2	23.9 9.6	53.3	42.9	87.5	81.6	99.0	44.9
T.S.	27.0 13.0	30.0 16.5	31.2 13.4	59.5	53.4	92.0	68.6	92.9	66.1
R.A.	34.1 14.6	37.6 17.4	34.5 18.1	99.1	87.1	61.4	71.6	91.9	107.9
MEAN	33.72 16.38	34.76 17.64	33.16 15.00	73.06	71.60	91.54	89.66	98.52	74.7
STAND. DEV.	6.23 3.73	6.70 2.79	6.82 4.11	18.25	21.96	20.80	23.78	18.00	23.64

TABLE III

DIFFUSING CAPACITY (DL), MEMBRANE DIFFUSING CAPACITY (Dm), AND PULMONARY BLOOD VOLUME - GROUP IIA

SUB-JECT	DL CON-TROL ***	DL ADREN-ALINE	DL ISU-PREL	Dm CON-TROL	Dm ADREN-ALINE	Dm ISU-PREL	Capillary Volume (Vc) CON-TROL	Capillary Volume (Vc) ADREN-ALINE	Capillary Volume (Vc) ISU-PREL
P.S.	19.6 12.1	22.5 11.1	22.7 9.6		47.5	54.1	84.4	56.3	48.6
F.C.	31.1 15.5	29.3 15.9	34.4 15.9	116.7	49.8	92.8	57.4	96.4	71.9
J.R.	22.7 8.6	15.7 9.0	27.2 15.1	113.4	24.4	42.9	37.8	60.2	99.9
M.L.	31.8 15.5	25.1 11.4	26.0 12.5	65.0	55.3	54.2	87.1	62.3	68.7
P.P.	37.1 21.5	32.8 15.6	41.7 22.9	56.9	73.5	68.2	142.6	83.2	147.8
E.B.	28.7 12.2	30.9 15.1	27.9 10.3	85.4	52.0	161.7	58.3	91.9	45.0
R.Y.	16.2 5.6	12.0 5.0	14.2 5.0	106.4	32.6	62.2	*	*	*
F.R.	32.3 12.8	25.7 12.2	**	124.4	56.8	**	60.1	64.8	**
S.S.	32.0 13.0	27.6 13.8	**	115.0	49.2	**	59.1	79.9	**
G.V.	30.1 14.9	*	29.8 12.8	57.0	*	92.9	83.8	*	61.4
L.D.	28.8 14.4	27.0 14.2	30.7 12.3	50.3	57.5	*	89.5	71.0	35.7
A.R.	18.9 7.6	14.7 10.5	16.7 7.3	47.7	*	47.6	38.7	106.7	36.2
MEAN	27.44 12.80	23.93 12.16	27.13 12.45	85.29	49.88	75.18	72.62	77.27	68.36
STAND. DEV.	6.49 4.20	6.93 3.27	8.04 5.03	30.48	13.56	37.1	29.66	17.1	36.06

*** Upper and lower rows on columns 2,3, and 4 represent DL value at low and high alveolar O_2 tension.
** Data not available
* Data not acceptable

TABLE IV

DIFFUSING CAPACITY (DL), MEMBRANE DIFFUSING CAPACITY (Dm), AND PULMONARY BLOOD VOLUME - GROUP IIB

	DL			Dm			Capillary Volume (Vc)		
SUB-JECT	CON-TROL	ADREN-ALINE	ISU-PREL	CON-TROL	ADREN-ALINE	ISU-PREL	CON-TROL	ADREN-ALINE	ISU-PREL
B.V.	26.7 16.6	25.7 11.0	26.8 11.9	36.2	73.0	72.4	133.1	55.9	60.0
E.B.	20.7 9.4	22.9 14.3	20.7 8.5	45.1	30.8	64.4	51.1	122	41.4
R.B.	19.6 7.4	19.3 6.8	19.5 7.5	79.9	102.6	75.3	35.6	31.4	38.0
H.M.	21.4 9.7	21.9 9.5	26.7 11.9	44.7	48.9	67.3	52.3	51.9	36.8
E.D.	29.3 11.0	29.4 12.9	27.1 11.2	*	78.8	100.1	49.7	67.2	61.3
D.T.	35.3 18.9	32.8 14.6	30.2 13.7	55.7	81.9	69.4	127.2	76.6	53.9
N.O.	26.5 11.9	27.9 12.6	25.5 11.4	59.2	61.3	55.7	64.0	68.1	75.1
D.F.	28.5 17.0	28.3 10.8	25.7 10.3	43.0	43.1	47.3	119.5	116.6	62.2
B.B.	27.9 10.0	28.3 10.8	25.6 10.3	*	*	100.0	43.9	48.5	119.3
R.R.	25.1 10.2	24.8 8.9	24.0 8.5	89.1	*	*	48.4	39.2	48.9
MEAN	26.10 12.21	26.13 11.85	25.68 11.23	56.61	65.05	72.43	72.48	67.74	59.49
STAND. DEV.	4.70 3.87	4.00 3.06	3.57 2.88	18.83	23.53	17.84	38.13	30.38	24.42

* Data not acceptable.

TABLE V

VITAL CAPACITY (VC), FORCED EXPIRATORY VOLUME AT ONE SECOND (FEV_1), PULMONARY PARENCHYMAL TISSUE VOLUME AND PULMONARY CAPILLARY BLOOD FLOW (QC) - GROUP I

	VC			FEV_1			TISSUE VOLUME(Vt)			QC		
SUBJECT	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL
A.R.E.	4334	4347	4279	2836	3203	3203	981	1273	981	3038	3011	3066
G.C.	5191	5154	5143	4566	4642	4644	1096	790	1495	*	3658	2192
L.C.	5044	4759	4945	2760	2707	2980	1362	1892	1111	3081	4725	9337
T.S.	3690	3829	3934	3121	2996	3197	861	685	685	*	*	*
R.A.	5212	4533	5151	4384	4508	4498	1156	777	560	7238	4859	1661
MEAN	4694	4524	4690	3533	3611	3704	1091	1083	966	4482	4063	4064
STAND. DEV.	666	491	552	872	898	798	189	507	369	2465	883	3562

* Data not acceptable.

TABLE VI

VITAL CAPACITY (VC), FORCED EXPIRATORY VOLUME AT ONE SECOND (FEV_1), PULMONARY PARENCHYMAL TISSUE VOLUME AND PULMONARY CAPILLARY BLOOD FLOW (QC) - GROUP IIA

	VC			FEV_1			TISSUE VOLUME (Vt)			QC		
SUBJECT	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL
P.S.	2518	3128	3074	1381	2176	2182	480	1023	1158	3211	5534	2713
F.C.	3074	3710	3435	1401	1718	1423	900	944	316	8333	**	2465
J.R.	3081	2688	3220	994	1080	1815	798	940	1076	**	5232	4281
M.L.	4084	4170	3967	1873	1851	1680	570	1101	1537	4840	2285	**
P.P.	4749	4857	4653	854	925	1405	862	638	1429	6848	6776	7528
E.B.	2969	3039	2449	1394	1697	1031	862	862	862	4699	6921	4742
R.Y.	2395	2209	2401	1032	1039	1028	600	1033	410	3894	*	3314
F.R.	3986	4053		2908	2210		552	1066	**	9922	1822	**
S.S.	3695	3799		2278	2590		1226	753	**	4436	**	**
L.D.	3759	3863	3608	1614	2031	1488	1544	588	862	**	2005	4696
A.R.	2712	2749	2620	867	1080	1059	653	653	364	4618	4981	3930
MEAN	3366	3479	3270	1509	1672	1457	822	881	890	5639	4444	4208
STAND. DEV.	+740	781	744	638	566	392	320	180	455	2100	2109	1590

* Data not acceptable.
** Data not available.

TABLE VI (Continued)

GROUP IIB

	VC			FEV_1			TISSUE VOLUME (Vt)			QC		
SUBJECT	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL	CONTROL	ADRENALINE	ISUPREL
B.U.	4016	3680	3935	1812	1568	1678	347	490	725	2803	1914	*
E.B.	1954	2248	2085	600	889	731	788	989	1077	3974	1817	1870
R.B.	1507	1513	1601	740	844	929	506	209	407	1786	4170	3290
H.M.	3017	3279	3553	1590	1889	1925	815	499	531	*	6378	8063
E.D.	3381	3413	3517	2712	2676	2834	415	445	433	1780	2892	3092
D.T.	3592	3696	3787	2742	2844	2879	981	704	662	4449	3292	5332
N.O.	3198	3322	3503	1112	1314	1567	950	297	341	4401	5912	4764
D.E.	3337	3301	3551	1860	1769	2285	727	625	984	*	3341	2392
B.B.	2125	1977	2257	1849	1593	1549	417	622	516	2029	2404	2898
R.R.	2787	2765	2966	1266	1304	2118	849	935	514	2236	*	2318
MEAN	2891	2919	3075	1628	1669	1849	670	582	619	2932	3568	3780
STAND. DEV.	± 796	760	810	730	668	714	226	250	245	1165	1639	1966

* Data not acceptable.

(Capillary blood flow less than 1500 cc/min.

TABLE VII

MEANS AND STANDARD DEVIATIONS OF ALL PULMONARY PARAMETERS - GROUP I, II

		GROUP I	GROUP II
DL_{CO}	CONTROL	33.72 ± 6.23 16.38 ± 3.73	26.79 ± 6.26 12.78 ± 4.09
	ISUPREL	33.16 ± 6.82 15.00 ± 4.11	24.50 ± 5.65 11.53 ± 2.76
	ADRENALINE	34.76 ± 6.70 17.64 ± 2.79	26.64 ± 6.53 11.45 ± 3.79
Dm	CONTROL	73.06 ± 18.25	73.17 ± 29.41
	ISUPREL	91.54 ± 20.80	60.56 ± 19.16
	ADRENALINE	71.60 ± 21.96	70.41 ± 30.95
Vc	CONTROL	89.66 ± 23.78	72.88 ± 32.79
	ISUPREL	74.70 ± 23.64	69.51 ± 22.43
	ADRENALINE	98.52 ± 18.00	69.63 ± 32.39
V.C.	CONTROL	4694 ± 666	3205 ± 808
	ISUPREL	4690 ± 552	3347 ± 825
	ADRENALINE	3611 ± 898	3102 ± 771
FEV_1	CONTROL	3533 ± 872 (75%)	1567 ± 697 (49%)
	ISUPREL	3704 ± 798 (79%)	1729 ± 689 (52%)
	ADRENALINE	3611 ± 898 (80%)	1568 ± 551 (51%)
Vt	CONTROL	1091 ± 189	735 ± 292
	ISUPREL	966 ± 369	751 ± 248
	ADRENALINE	1083 ± 507	728 ± 385
QC	CONTROL	4482 ± 2465	4368 ± 2245
	ISUPREL	4064 ± 3562	4092 ± 1999
	ADRENALINE	4063 ± 883	3869 ± 1599

TABLE VIII

MEANS AND STANDARD DEVIATIONS OF ALL PULMONARY PARAMETERS GROUPS I, IIA AND IIB

		GROUP I	GROUP IIA	GROUP IIB
	CONTROL	33.72 ± 6.23 16.38 ± 3.73	27.44 ± 6.49 12.80 ± 4.20	26.10 ± 4.70 12.21 ± 3.87
DL_{CO}	ISUPREL	33.16 ± 6.82 15.00 ± 4.11	23.93 ± 6.93 12.16 ± 3.27	25.68 ± 3.57 11.23 ± 2.88
	ADRENALINE	34.76 ± 6.70 17.64 ± 2.79	27.13 ± 8.04 12.45 ± 5.03	26.13 ± 4.00 11.85 ± 3.06
	CONTROL	73.06 ± 18.25	85.29 ± 30.48	56.61 ± 18.83
Dm	ISUPREL	91.54 ± 20.80	49.88 ± 13.56	72.43 ± 17.84
	ADRENALINE	71.60 ± 21.96	75.18 ± 37.1	65.05 ± 23.53
	CONTROL	89.66 ± 23.78	72.62 ± 29.66	72.48 ± 38.13
Vc	ISUPREL	74.70 ± 23.64	77.27 ± 17.10	59.49 ± 24.42
	ADRENALINE	98.52 ± 18.00	68.36 ± 36.06	67.74 ± 30.38
	CONTROL	4694 ± 666	3366 ± 740	2891 ± 796
V.C.	ISUPREL	4690 ± 552	3479 ± 781	3075 ± 810
	ADRENALINE	4524 ± 491	3270 ± 744	2919 ± 760
	CONTROL	3533 ± 872 (75%)	1509 ± 633 (45%)	1628 ± 730 (56%)
FEV_1	ISUPREL	3704 ± 798 (79%)	1672 ± 566 (48%)	1849 ± 714 (60%)
	ADRENALINE	3611 ± 898 (80%)	1457 ± 392 (45%)	1669 ± 668 (57%)
	CONTROL	1091 ± 189	822 ± 320	670 ± 226
Vt	ISUPREL	966 ± 369	881 ± 180	619 ± 245
	ADRENALINE	1083 ± 507	890 ± 455	582 ± 250
	CONTROL	4482 ± 2465	5639 ± 2100	2932 ± 1165
QC	ISUPREL	4064 ± 3562	4444 ± 2109	3780 ± 1966
	ADRENALINE	4063 ± 883	4208 ± 1590	3568 ± 1639

CHAPTER V

DISCUSSION

Because of the sensitivity of techniques used, a discussion of potential sources of error and hence of the accuracy of the obtained results is essential. An outline of possible instrumental and physiological sources of variability in the recorded values follows:

1. Our subjects usually had changes in their recorded vital capacity throughout the testing day. Adrenaline and Isoproterenol (Isuprel) were expected to do this; however other factors influencing the performance of the vital capacity manoeuver such as motivation or general fatigue of the patient, as well as physiological variations in the dynamic state of their asthma, unrelated to drugs, may have been contributory to a variation in response throughout the seven hours of testing and observation.

2. A potential source of error is difficulty in accurately defining inspiratory time on the spirogram. In normal subjects and in asthmatics with mild air way obstruction, the transition between inspiration and breath holding is obvious on the tracing. However in those patients with moderate to severe air way obstruction inspiration is prolonged and the spirometric tracing obtained shows a gradual change from the inspiratory to the breath holding segment; making objective separation of these two elements difficult. In such patients the tendency is for effective breath holding to be overestimated and therefore for D_L to be underestimated.[94]

3. Since the time interval between each of the trials was 10 to 15 minutes, and carbon monoxide washes out in less than 10 minutes, build up of carbon monoxide is unlikely but could conceivably have slightly decreased the DLCO in the final trials of each set of tests.[129]
4. A variation in vital capacity of our patients, previously mentioned, besides directly effecting diffusing capacity by altering membrane area, also changes the relative point of sampling during expiration. An electrical switch was set to be activated following the exhalation of the initial 1200 milliliters of the expirate (this point was determined by three or four vital capacity manoeuvers performed prior to the administration of Adrenaline or Isoproterenol). Consequently, if the subject, because of lack of motivation or fatigue, did not obtain the same magnitude of vital capacity in any of the trials, the expiratory sample could conceivably have been contaminated with dead space air and the sample would not be truly representative of alveolar gas.
5. In the calculation of DM and Vc by use of the measurement of diffusing capacity at low and high oxygen tensions, the following assumptions have been made:
    a. a variation in alveolar oxygen tension does not change DM and Vc.
    b. DLCO is measureable with accuracy at different alveolar oxygen tensions.

c. the values of theta are accurate.

Although proof is lacking for the assumption that oxygen inhalation, even for short periods of time, does not alter the membrane component of the diffusing capacity, all investigators using these techniques have accepted this. The second assumption, implying that hyperoxia does not disturb diffusing capacity is perhaps dubious for the normal lung and certainly extremely unlikely in the asthmatic lung which has been demonstrated to have gross basic derangements of the ventilation perfusion ratio which in turn, of course, unfortunately effects DL. Finally, although the value of theta at higher oxygen levels appears to be satisfactory, when the alveolar oxygen tension is below 150 mm. of mercury it is not precisely known and this results in a distortion in the regression line which determines DM and Vc. [105]

6. The membrane diffusing capacity is very sensitive to the value of lambda used in the computation. Since there is uncertainty as to the true value of lambda in vivo, an assumed lambda value of 2.5 merely represents a reasonable practical approximation of diffusing capacity.[105] Examination of the graph of 1/DL against 1/θ (Figure 7) reveals that when the intercept of the extrapolated regression line on the "Y" axis is close to the origin, a small error in the estimation of DL can lower the intercept to the origin or below producing estimates of DM which are infinite or negative. In the present

investigation we had two negative and one extremely high DM value among eighty determinations of membrane diffusing capacity. These results are comparable to those of other investigators. [105]

7. We have corrected our DLCO's for the level of hemoglobin in the venous blood, although this correction ideally should be made by the hematocrit of the pulmonary capillary blood. Since such a correction was not possible, despite the fact that there is evidence that the pulmonary hematocrit value is approximately 10-15 per cent less than the systemic venous hematocrit,[132] we have accepted, as have others, only venous hemoglobin correction.[20]

8. During the breath holding period there is a tendency for a subject to do a Valsalva manoeuver in order to maintain constant alveolar volume. The effect of this manoeuver would be to decrease capillary blood flow secondary to decreased venous return resulting from the increase in intrathoracic pressure.

9. Inspection of the equation used in the calculation of pulmonary parenchymal tissue volume indicates that small experimental errors in the determination of the intercept or the acetylene disappearance curve with the "Y" axis is magnified immensely when the value of V_T is computed. For instance a 10 to 15 per cent increase in the value of the intercept almost doubles the calculated value of V_T.

10. Oxidation of the filament in the thermal conductivity cell of the gas chromatograph upon exposure to a high concentration of oxygen may gradually reduce the sensitivity of this unit. However, this reduced sensitivity would appear to be symmetrical and since control values were done on each day for each set of our determinations, should not have effected our results. It is, we believe, noteworthy that our present filament has performed satisfactorily for over one hundred determinations despite warnings from the chromatograph distributor that it could not perform at over a 21 per cent oxygen level for more than a few exposures.

Some of earlier results with the initial Microtek sampling valve (subsequently substituted for by a Beckman sampling valve) showed values of acetylene in samples obtained after long breath holding test which were higher than the values of acetylenes following short breath holding in the same patient. This is, of course, physiologically unexplainable. It was suggested that the grease used within the apparatus may have been absorbing and subsequently releasing acetylene thereby confusing readings. However, three separate calibration curves, carried out subsequently have shown a completely linear response except at very low concentrations of acetylene. These aberrations were not sufficient to explain a wide scatter of results in Qc. These then have been the principle sources of instrumental and mathematical errors in this investigation.

An evaluation of diffusing capacity, pulmonary capillary blood volume and flow following bronchodilator administration was made in this study. These parameters were of particular interest because of the recent documentation of increased imbalance in ventilation perfusion ratios during exacerbations of bronchial asthma[11] and also of increased hypoxia following bronchodilator administration.[66,116]. This paradoxical drop in oxygen saturation in the face of the improved ventilation resulting from bronchodilator use suggested a bronchodilator may increase the severity of a distribution disturbance in asthmatic patients.

An evaluation of the effect of Isoproterenol on normal as compared to asthmatic subjects[66] showed that, in the normal individuals, the drug provoked no essential change in A-a oxygen gradient, and in diffusing capacity, while in the asthmatic subjects the A-a gradient widened significantly and the diffusing capacity dropped slightly. The response of the asthmatic to Isoproterenol would therefore appear to be an exaggeration of previously imbalanced V/Q ratio related in part to preferential delivery of medication to areas already well ventilated with more imbalance of air to blood distribution particularly if regional increase in blood flow occurs in relatively underventilated areas.

One-third of the asthmatic patients studied by Tai and Read[116] were demonstrated to show a drop in arterial oxygen tension following the inhalation of Isoproterenol (Isuprel) which they concluded

to be as the result of reversal of pre-existing, compensatory, regional pulmonary vasoconstriction. The vasodilator actions of isuprel are therefore theoretically implicated in these observations. It is noteworthy however, that administration of Adrenaline[126] has been demonstrated to be followed by decreases in oxygen saturation suggesting the development of ventilation perfusion impairment unassociated with pharmacological vasodilatation.

All such observations must be interpreted in the light of evidence of gross impairment of ventilation as related to perfusion in the asthmatic state itself. Radioactive xenon studies of asthmatic subjects during state of remission by Bentivoglio et al[11] have shown marked regional abnormalities of ventilation - attributed by them to patchy atelectasis. Beale, Fowler and Comroe[124] have shown an under-ventilated slow compartment (in terms of the ratio of ventilation to lung volume) of appreciable magnitude in symptom free asthmatics.

During acute exacerbations of asthma a discrepancy between alveolar ventilation and minute ventilation, attributed to preferential distribution of inspiratory air to more patent air ways has been documented by McFadden and Lyon[83]. Their calculations indicate that the more open air ways occupying about one-quarter to one-half of the lung volume receive about four-fifths of ventilation and this, of course, eventuates in a small area of over ventilated and under pertused lung with a larger area

of under ventilated and over perfused lung. This situation may be, in part, compensated for by a gross alteration in perfusion which, at any rate as reflected by macroaggrogate scanning techniques, becomes extremely deranged during an asthmatic exacerbation.[127]

All of the above observations led us to anticipate appreciable differences between our normal and asthmatic subjects particularly in their respective responses to Adrenaline as compared to Isuprel. All of the parameters measured by us should have been affected by ventilation and by the relationship between ventilation and perfusion which, as outlined, would appear to be appreciably altered in the asthmatic subject to whom a broncodilator is administered.

The commonest method of assessing response to a bronchodilator is to make measurements of vital capacity and of expiratory air flow (the forced expiratory volume in 1.0 second being a very commonly used index of this) before and from 5 to 15 minutes following administration of the drug. It has recently been pointed out[93] that the maximum response occurs at from 20 minutes to 1/2 hour following administration. Therefore in our investigation in which testing was carried out from 20 minutes to 1 1/2 hours following administration of the drug the bronchodilator effect should have been evident. Averaging later values, influenced by fatigue and decline in pharmacological effect of medicine with earlier ones when response might have been evident, may have resulted in effective cancellation of these various factors.

Factors of fatigue, boredom and motivation, may have become important in these patients as by the nature of the testing procedure a total of seven hours was required before the determinations were completed. A total of twenty-two forced expiratory manoeuvers were carried out and pure oxygen was breathed for at least 60 minutes on each testing day. The oxygen was complained of because of its drying effect which could certainly have caused some air way irritation mitigating against the effect of bronchodilators. Pure oxygen has also been implicated in provocation of regional microatelectasis and a non-specific metaplastic change in air ways[131] but it seems unlikely that this could have occurred within this period of time.

It is noteworthy that the majority of patients volunteered that their breathing was subjectively improved following bronchodilator administration. It is conceivable that it it had been possible to do mechanic studies, more subtle changes in air way resistance, masked by the forced expiratory manoeuver, might have been demonstrated.[130]

A difference in tissue volume, the presumed quantity of lung substance in which acetylene was being incorporated during the testing procedure, was not anticipated between normals and asthmatics or in either group following a bronchodilator. Although there is some suggestion that one group of asthmatics may have demonstrated some slight decrease in tissue volume this was not a statistically signiticant finding.

As expected, the diffusing capacities of the asthmatic patients were less than those in normal individuals although not markedly so and this corroborates the fairly generally held impression that the DLCO is not markedly affected in asthma as compared to emphysema.[7,9]

However, contrary to our preconceived ideas, no appreciable change was demonstrated following the administration of either adrenaline or Isuprel in normal or in asthmatic individuals.

On theoretical grounds we expected to observe an increase in DL, DM and QC following the administration of adrenaline and an increase in all three parameters as well as in capillary blood volume after the administration of Isoproterenol. The membrane component of the diffusing capacity was expected to go up because of opening of new alveoli with bronchodilatation and because of improved ventilation in those alveoli previously poorly aerated - therefore exposing more alveolar surface to process of diffusion. When Isuprel had been used it was anticipated that the diffusing capacity would increase, in addition, because of an increased capillary blood volume secondary to vasodilatation.

In view of the fact that both Adrenaline and Isoproterenol have a positive chronotropic effect, (increasing the rate) and a positive inotropic effect, (increasing the force of myocardial contraction) we anticipated an increase in pulmonary capillary blood flow with both drugs.

One might speculate that a change in the effective surface area brought about by bronchodilatation from Adrenaline, which would in turn have increased DM, might have been effectively counterbalanced by a decrease in capillary blood volume secondary to the vasoconstrictor effect of this medicine. Our results, however, demonstrated no measureable change in either DM or VC so this explanation appears untenable.

The pulmonary capillary blood volume, as measured by us, did not appear to change significantly following Isuprel administration and it is, of course, possible that this was the situation - pulmonary capillary blood volume does not change significantly following this drug, or that we did not give enough drug for a long enough time to these particular patients to provoke a change. There are, however, some technical details connected with the manoeuvers used in making our determinations which may, also, have affected the results.

It has been generally recognized[125] that hypoxia will cause pulmonary venoconstriction this being, up to a point, a protective mechanism shunting blood away from underventilated areas and thereby adjusting the ventilation perfusion ratios.

In this particular investigation, in order to determine DM and VC, the diffusing capacity is measured at high and low oxygen concentrations with the high level being attained by the breathing of pure oxygen for 15 to 20 minutes. Following the inhalation of Adrenaline or Isoproterenol

oxygen, once again, was administered for 15 to 20 minutes. As a result there is an almost total washout of alveolar nitrogen and a considerable increase in the alveolar and arterial oxygen tensions. (500-600 mm.Hg.) It is possible that the resulting high arterial oxygen could virtually eliminate efferent vasoconstrictor stimuli and could conceivably prevent a normal vaso-active response in these vascular units. Therefore there is a possibility that the necessary administration of oxygen throughout the testing procedure could have resulted in a partial functional paralysis of pulmonary vascular units and a dampening of the normal vaso-active response. This sort of phenomenon should increase measured capillary volume - both under baseline conditions as well as following drug administration and might therefore not be picked up as any sort of a change.

The measurements of pulmonary capillary blood flow obtained by us were most unsatisfactory and the causes of possible error in this determination have been previously outlined. We therefore had a wide scatter of results even in the normal individuals. As has been elaborated upon extensively previously the pulmonary diffusing capacity and its components (DM and Vc) as well as pulmonary capillary blood flow are highly sensitive to the relationship between ventilation and perfusion. In the finaly analysis the uptake of carbon monoxide used for the measurement of DL and of the acetylene used for the evaluation of QC are

functions of the V/Q ratio rather than representative of the absolute values of these parameters individually.

In essence then by utilizing the specified single breath technique of Ogilvie we were unable to demonstrate any significant changes in pulmonary diffusing capacity, pulmonary capillary blood volume or pulmonary capillary blood flow following the administration of 15 breaths of Isoproterenol or Adrenaline to a group of 22 asthmatic and 5 normal subjects.

CHAPTER VI

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSIONS

Pulmonary diffusing capacity,(DL), membrane diffusing capacity (DM), pulmonary capillary blood volume (Vc), pulmonary parenchymal tissue volume (Vt) and pulmonary capillary blood flow (Qc) appeared to be unchanged following the administration of Isoproterenol and Adrenaline to twenty-two asthmatic and five normal subjects.

The parameters were measured utilizing the single breath technique of Forster as modified by Ogilvie. The procedure required the patient to perform at least 18 separate breath-holding manoeuvers over a period of 4-5 hours.

Despite the fact that the 15 "puffs" of Adrenaline and separately of Isoproterenol which were nebulized to these patients have been demonstrated to be therepeutically effective and over half of them volunteered that a sensation of improved ventilatory capacity was produced, no statistically significant objective change in ventilatory capacity was recorded. This was, we believe, related to the techniques of spirometric recording and to the large number of expiratory manoeuvers required over a period of time.

As expected there were differences between the recorded vital capacities, expiratory rates of air flow, and diffusing capacities in the normal as compared to the asthmatic individuals. Disproportion in the relationship between ventilation and perfusion appeared to be the most likely cause for this observed decrease in diffusing capacity.

Membrane diffusing capacity appeared to drop following the administration of bronchodilator in only one group of subjects (Group IIA), who were asthmatic individuals to whom Isoproterenol had been given prior to the subsequent administration of Adrenaline. We suggest that a more pronounced increase in blood flow in this particular group may have caused more of a venous admisture effect with a more gross distortion of ventilation perfusion ratio and hence the recorded decrease in the membrane diffusing capacity.

The nature of this particular technique of estimating pulmonary circulation and the transfer factor is such that it would appear to be only applicable to relatively stable conditions.

Out investigation indicates this technique is not appropriate for the analysis of rapidly changing responses in the lung. This is because the technique itself involved the making of repeated measurements over a relatively long period of time during which the assumption is made that there is no alteration in the characteristics of the alveolar capillary membrane or in the homogeneity of ventilation and/or blood flow. Such an assumption is particularly invalid for a disease such as asthma in which a temporal variation in all of these factors might theoretically occur.

An analysis of such possible alterations has not been carried out in any definitive fashion. As pointed out, the particular kind of measurements which we made in this investigation do not adequately reflect the alterations which must be occurring. A study which does reflect such changes needs to be done.

Some technique such as radioactive scanning, by which rapid variations in regional ventilation and perfusion can be delineated, would appear to be necessary for analysis of the complex pathophysiological alterations which occur in asthma

In conclusion, an investigation of the effects of Adrenaline and Isoproterenol on some aspects of ventilation, gas exchange and pulmonary circulation failed to reveal any significant change following the administration of therapeutic doses of these drugs.

APPENDIX A

GAS CHROMATOGRAPHY

FIGURE 4
MICROTEK GAS CHROMATOGRAPH GC 2013 M

GAS CHROMATOGRAPHY[50,98]

Chromatography is the term applied to a physical method of separating a mixture into its components. The components are distributed between two phases, one of which is stationary and has a large surface area. The other is the moving phase; it contains the mixture to be separated and it percolates through the stationary phase. The components that are more strongly attracted to the stationary phase move more slowly, so that separation is accomplished as the mixture is carried through the system.

The term "chromatography" was originally used in 1906 by Tswett, a Russian biologist, for separation of colored pigments from chlorophyll. The term is a misnomer when applied to the colorless material and the misnaming is more obvious when applied to the separation of gases, since they are not only colorless but also invisible under normal conditions.

According to the nature of stationary phase which can be either a solid or a liquid, and the moving phase that can be either a liquid or a gas, four types of chromatography may be visualized:

1. liquid-solid
2. liquid-liquid
3. gas-liquid
4. gas-solid chromatography.

Some of the advantages of gas chromatography are its speed of analysis, versatility of application and simplicity of operation. Also, all gases which are useful in cardio-pulmonary physiology can be separated and analysed with a single instrument.

The major elements of a gas chromatographic system include: a. a carrier gas, b. a device for injecting a sample into the carrier gas flow, c. a column or columns containing suitable packing material, d. a thermostatically controlled oven to keep the temperature surrounding the columns constant, e. a detector which is thermostatically controlled, f. sensitive strip chart recorder.

Carrier gas. Thermal conductivity detectors may use a wide variety of carrier gases, but hydrogen, helium, argon and nitrogen are preferred. The carrier gas should not be used for analysis; it should not be absorbed by the packing material of the column and finally should not harm the detecting system.

As sensitivity, analysis time and separation of gases are all altered by changes in flow of the carrier gas, the glow should be carefully adjusted and maintained within a variation of less than one percent. A dry filter will remove the impurities of the gas. As small changes in ambient temperature can potentially lead to a very large change in the flow of the carrier gas, the temperature should be thermostatically controlled.

Injection device. The aim is to inject an aliquot of the sample into the carrier gas stream in a quantitatively reproducible manner. There are various techniques for introducing samples into the gas chromatograph, one of which is through pneumatic operation of a constant volume sampling valve which will reduce many of the sampling errors.

Columns and packing materials. Columns may be made of glass, brass, copper, aluminum or stainless steel, but the latter is preferred as it is non-corrosive and is physically flexible. The materials used for packing the columns in gas solid chromatography include silica gel, activated charcoal, alumina and molecular sieves (aluminosilicates).

There is an optimum length for the column used to separate specific gas components. If the column is too short, the components will be incompletely separated and their response curves will overlap. If the column is too long the peaks will be broad and more difficult to measure accurately, and also with such a column there will be an unnecessary delay in the appearance time.

The retention time of the column, which is defined as the time taken for the gas mixture to traverse the column, is a function of many factors but is primarily influenced by the rate of carrier gas flow, the greater the flow, the shorter the retention time.

Retention volume is the constant product of the flow rate and the retention time, if the retention volume of two gases is similar, their respective peakes will be close and may overlap.

As was mentioned earlier, several materials have been used to pack the columns. Successful separation of certain gases is accomplished by the use of special stationary phases which have a "pore" structure of molecular size. The pores permit the separation of gases according to their shape and molecular size as the gases are carried through the column. As molecular sieve columns trap carbon dioxide and water vapor, after prolonged exposure to these materials the columns become contaminated and lose their ability to separate other components.

Thermostatically controlled oven. It is usually recommended to use a column chamber or an oven, the temperature of which is kept constant by the use of a thermostat. Constancy of temperature within one degree centigrade is satisfactory.

In analysing a gas mixture at a constant temperature, the first peaks to be eluted are high and narrow, while if retention times are great, the last peaks will be low and wide. This problem may be eliminated by increasing the temperature of the column during the course of the analysis so that the initial temperature will be sufficient to produce reasonable shapes for the initial peaks, and the final one high enough to allow the elution of the last peaks within a reasonable time.

Detectors. There are several techniques for the detection and measurement of the gases as they are eluted from the column in a gas chromatograph. Respiratory gases are most often measured by determining their effect on the thermal conductivity of the carrier gas.

Thermal conductivity of a gas is its capacity to conduct heat It varies with different gases. Thermal conductivity changes in the gases eluted from a column are detected with a thermistor located at the outlet of the column. Thermistor has a high thermal coefficient of resistance and its electrical resistance changes markedly with small changes in the temperature. With the application of electrical current to a thermistor, it becomes warmer than the gas surrounding it and heat is conducted away at a rate dependent on the thermal conductivity of the gas. When thermistor is surrounded by pure helium , because of the high thermal conductivity of helium the heat transfer is very efficient and the thermistor heats up only slightly. When some other gas is mixed with the helium, the thermal conductivity is reduced and consequently the thermistor temperature will rise. This rise in temperature will increase the electrical resistance of the thermistor which in turn can be measured and related to the concentration of the other gas.

Chart Recorder. The prime characteristic of a suitable

recorder is a rapid response curve and a full scale deflection from an input of one millivolt. A great variety of recorders are at present available.

APPENDIX B

CALCULATIONS

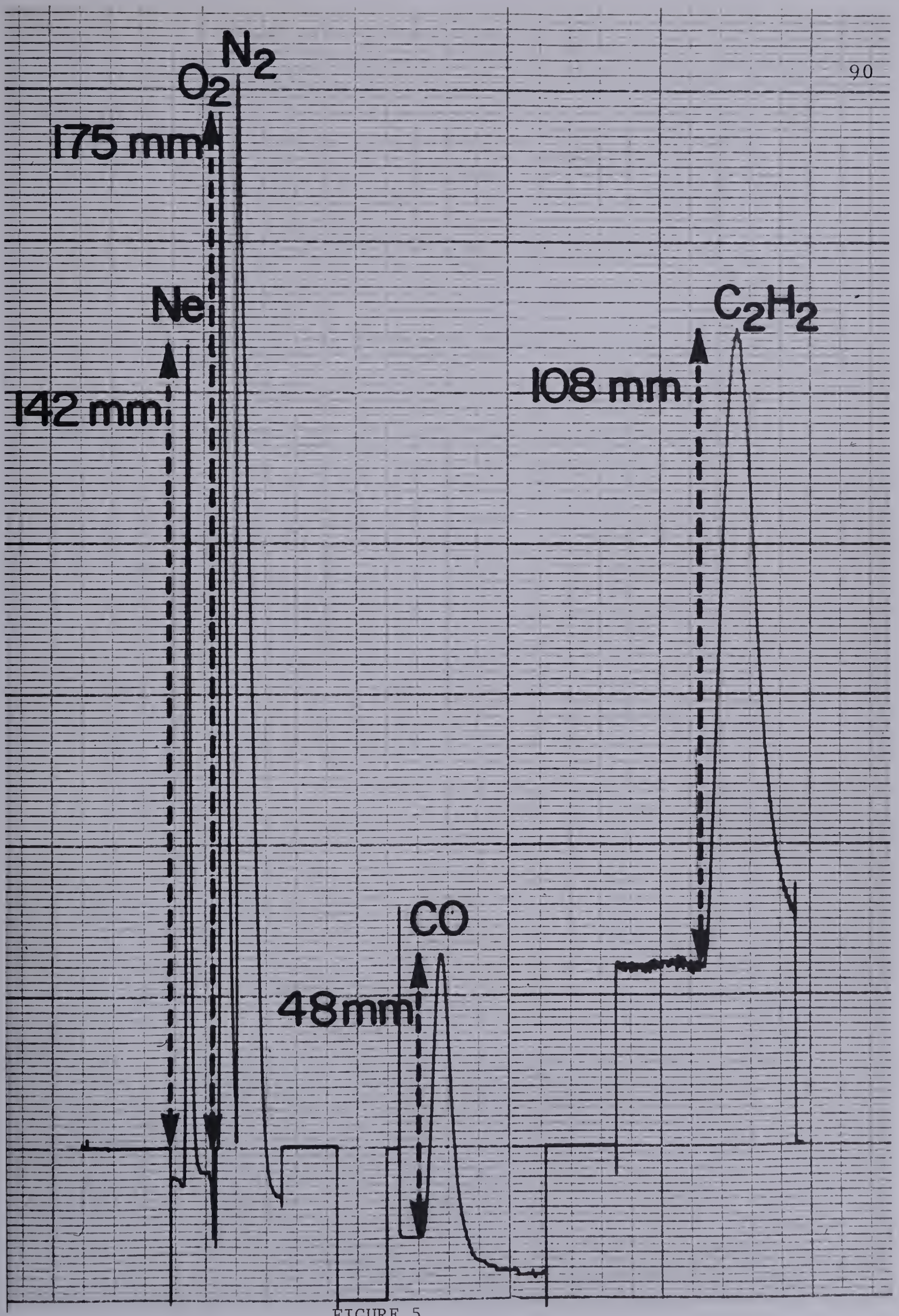

FIGURE 5

SAMPLE CHROMATOGRAM REPRESENTING PEAK HEIGHTS OF NEON, OXYGEN CARBON MONOXIDE AND ACETYLENE

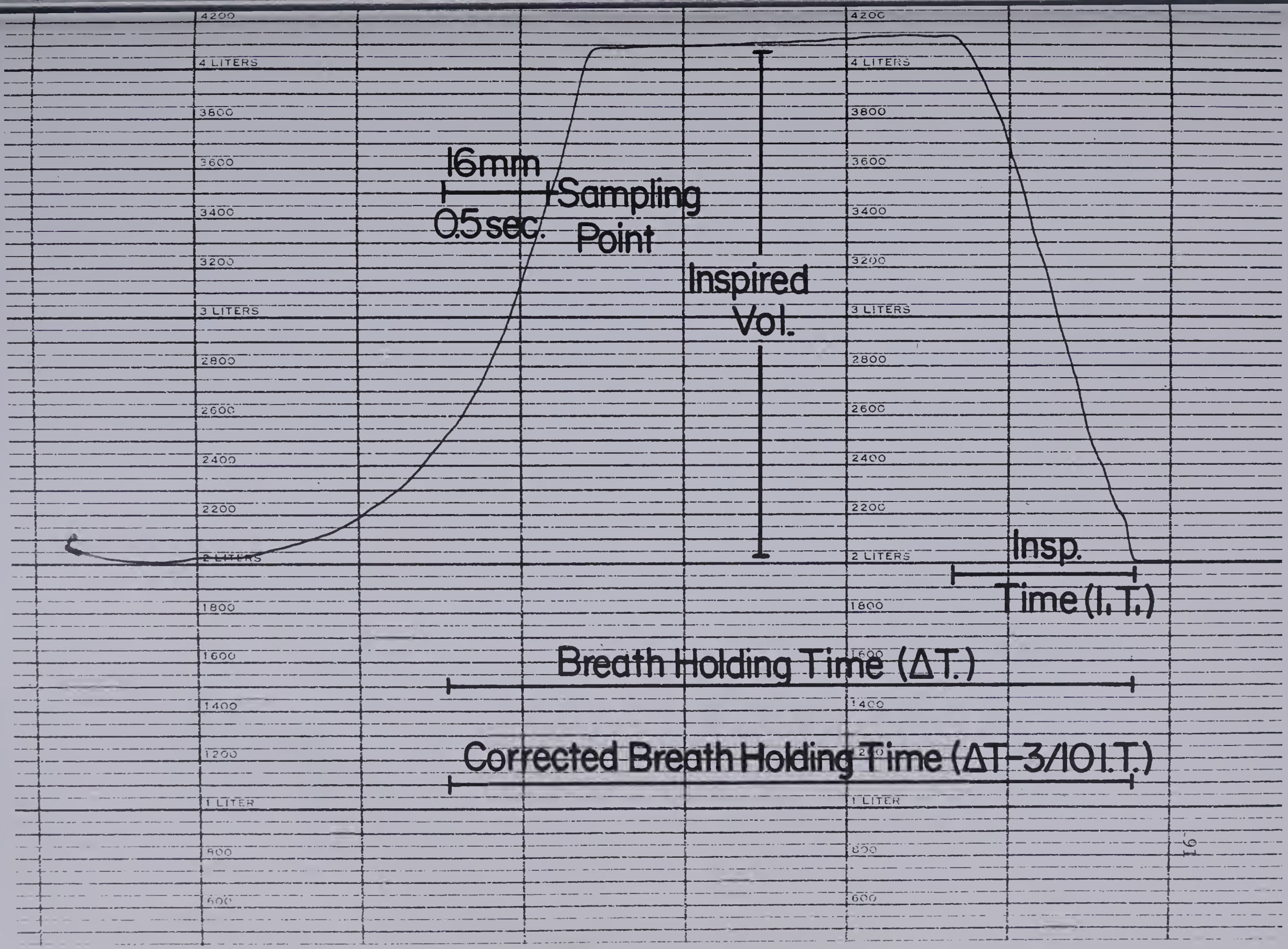

FIGURE 6
SAMPLE SPIROGRAM

CALCULATIONS

The necessary raw data includes the values of the peak heights of Ne, O_2, CO, and C_2H_2 (Figure 5) and values for inspiratory volume and breath-holding time. The latter is determined by measuring the time from the beginning of the inspiration to half a second following the point of sampling in expiration, and from this value, one third of inspiratory time is subtracted (Figure 6). The result is used as corrected breath-holding time which is integrated in the equations for diffusing capacity and capillary blood flow. The above modification in the calculation of breath-holding time is necessitated by the theoretical and experimental analysis which is made by Jones and Mead[62,63] of anomalies in the estimation of single breath DLco.

Also required as raw data are: patient's vital statistics, values of ambient temperature and barometric pressure for the determination of STPD factor and values of low and high oxygen concentration. The data sheet at the end of this appendix reveals a sample of input data.

The above data are required for the execution of fairly complex mathematical equations which are integrated in the APL (a program language) of the 360 computer currently used at the University of Alberta.

Inspired volume is measured on the spirogram, and alveolar volume is calculated by the dilution of the inert gas, (Neon) in

alveolar air. Alveolar O2 tension is calculated by consideration of barometric pressure and the ratio of expiratory over inspiratory oxygen concentration. Intracorpuscular oxygen tension necessary for the calculation of theta is approximated by subtracting five mm Hg from the value of Alveolar oxygen tension[105]. DL is calculated from the alveolar volume (VA) during breath holding and the slope of the line of CO disappearance, ($\frac{\text{Ln (FACO - O/FACo)}}{\text{t}}$) where t is the time of breath holding, FACO-O and FACO - t represent alveolar fraction of carbon monoxide at time zero and time -t respectively. FACO-O is estimated from inspiratory carbon monoxide concentration with consideration of dilution of Neon in the alveolar sample.

Dm and Vc may be calculated by solving the simultaneous equations relating $1/\theta$ to 1/DL, if DL and 0 are known. θ is a function of intra-corpuscular O_2 tension and for (ratio of permeability of the red cell membrane to that of the red cell interior) = 2.5, the following relationship has been proposed by Roughton and Forster $1/\theta = 0.73 + 4.4\ PO_2$ where PO_2 is the intracorpuscular oxygen tension in atmospheres.

For these calculations to be valid it must be assumed that Dm and Vc remain constant at the different oxygen tensions. This is considered to be true as long as the capillary blood flow remains the same during both measurements.

Calculation of Vc and Dm may be performed manually by plotting reciprocal values of DL on the "Y" and reciprocal values of θ on the "X" axis. Extrapolation of the regression line on "Y" axis determines the intercept, the values of which would be reciprocal of Dm and the slope of regression line determines the reciprocal of Vc.

Conventionally the value of $\lambda = 2.5$ has been accepted as standard and calculation of 0 are made on this basis.

Lambda (λ) equals D_2/b_2 divided by D_1/b_1, where D_1 and D_2 are the respective diffusion coefficients of carbon monoxide in the red cell interior and in the red cell membrane, and b_1 and b_2 are the respective thicknesses of the red cell interior and the red cell membrane.[105]

The effect of variations in the value of on Dm and Vc has been graphically demonstrated by Roughton.[105] For $\lambda = 1.5$ the intercept will become smaller (closer to zero point) and the slope of the regression line will be steeper; consequently the value of Dm will be larger and Vc will have a smaller value. Inversely for $\lambda = \infty$, Dm and Vc will be respectively smaller and larger than the same parameters on the basis of $\lambda = 2.5$.

It has to be emphasized that Dm is much more sensitive than Vc to the particular value of theta used in the computation. The range of variations in Roughton's experiments has been up to 30-40 per cent. Because of the relative insensitivity of Vc to the values of θ, this datum, Vc, is more reliable.

It has to be stated that in the calculations of Dm and Vc, assumptions have been implicitly made that the distribution of capillary blood volume and diffusing capacity to alveolar volume is uniform. These assumptions are probably reasonable in normal subjects. In patients with pulmonary disease the above assumptions are not necessarily true. Unfortunately, however, from a technical point of view there is no simple, practical way, at present, to eliminate this source of error.

Tissue volume of the lung which is a function of the intercept of the Acetylene disappearance curve is extremely sensitive to the errors of the estimation of this intercept. Variation of 10% to 15% in the C_2H_2 intercept will result in approximately 100% change in Vt in the same direction. Consequently it is imperative to do as many trials as are practical and obtain as many points on the coordinate of natural logarithm of Acetylene disappearance versus time. This will result in a more accurate regression line by the least square technique, and a more accurate intercept, andwill prevent gross errors in the estimation of pulmonary parenchymal tissue volume.

It is evident that any small errors in the calculation of Vt would magnify the corresponding error in the value of pulmonary capillary blood flow. This can be easily appreciated by the examination of the equation which is used to compute this parameter.

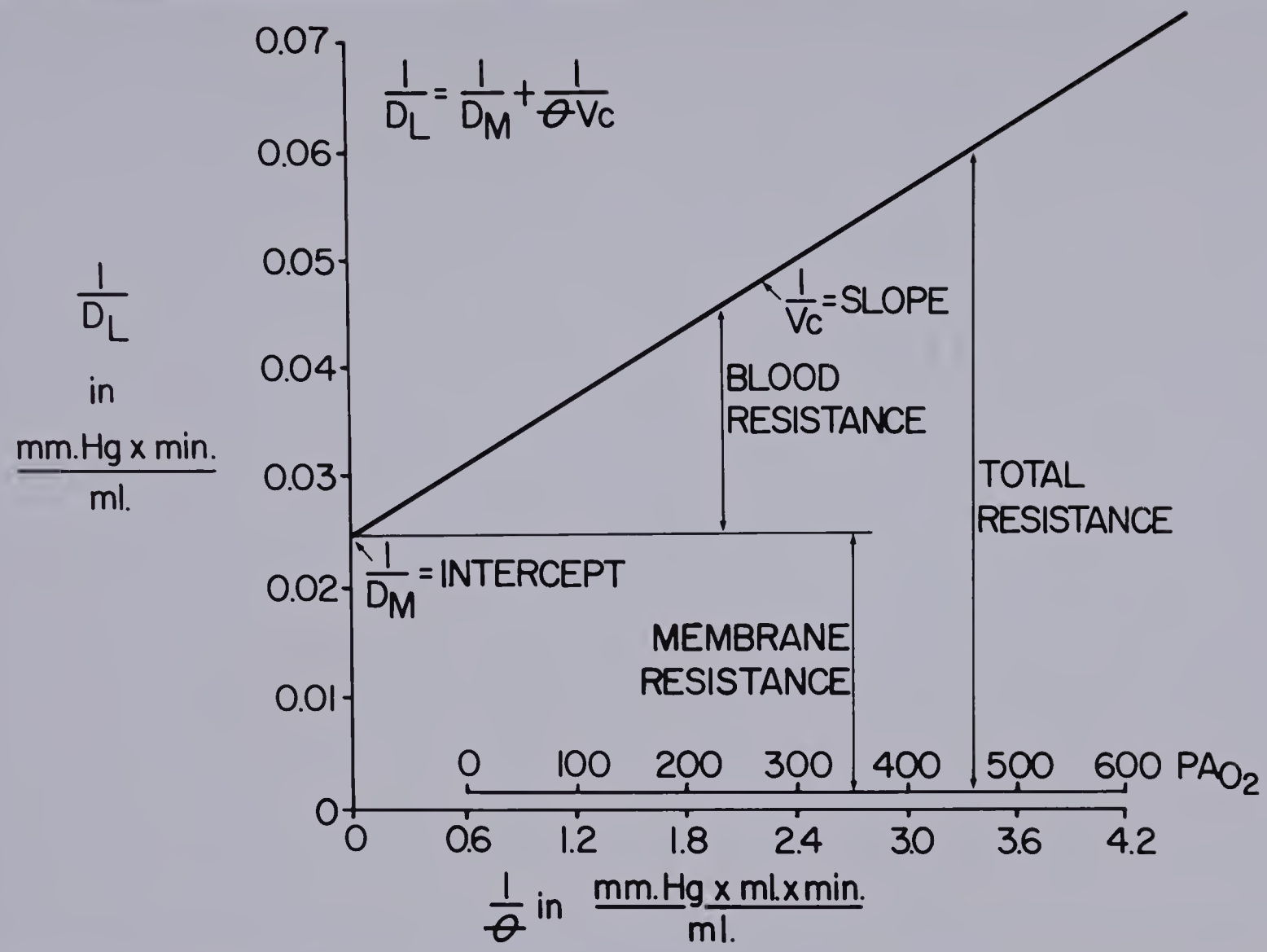

Figure 7
GRAPHIC DETERMINATION OF PULMONARY CAPILLARY BLOOD VOLUME AND MEMBRANE DIFFUSING CAPACITY FROM LEWIS ET AL [76]

DATA SHEET

NAME A. R. Esfandiary DATE May 8, 1968

AGE 29.8 WEIGHT 145 HEIGHT 71"

PB (mmHg.) 710 STPD FACTOR 0.832

Low and high tank O_2 in % 20.4 & 95

Exp. 1 Bag	Ne	O_2	FEV_1	CO	C_2H_2	BHT	V_I
Alveolar	162.5	219	2910	62.5	78	6.87	4697
Exp. 2 Bag							
Alveolar	163	212	2910	59	77	7.69	4292
Exp. 3 Bag							
Alveolar	159	209	2868	48	77	10.22	4333
Exp. 4 Bag							
Alveolar	169	215	2394	61	75	8.00	4457
Exp. 5 Bag							
Alveolar	171	213	2683	81	-	8.78	4003
Exp. 6 Bag							
Alveolar	146	219	2868	77	-	8.22	3631

Before	X
After	

Medication

	Ne	O_2	N_2	CO	C_2H_2
Control Exp 1 - 4	232.5	243		153	130
Control Exp 5 - 6	248.5	227		176.5	

APPENDIX C

COMPUTING PROGRAMING

A computing program in "APL" (a program language) has been developed to execute the mathematical statements, necessary for the calculation of the required pulmonary parameters.

The University of Alberta is one of the universities in North America to initiate this language and is presently one of several universities in Canada to use it as an active computing language. We have used "APL", because of the simplicity of the language and the availability of the computer terminal at the University of Alberta Hospital.

The prime advantage of "APL" is that immediate access to the computer can be made via a typewriter terminal. The language is concise and very powerful in efficiency of use. At present the computer is available three hours a day and is used in a time sharing mode.

"APL" is called "conversational" computing, because the user can get immediate response from the computer when he is submitting data or when he is writing, correcting or executing a program. A full range of error messages from the computer immediately and automatically inform the user of any mistake and the type of error.

Symbols used in "APL" consist of nine numerics, twenty-six alphabetics and fifty-two special characters, all of which appear on the typewriter keyboard.

One of the advantages of "APL" is that it is easy to learn. The program when written, illustrates quite clearly the mathematical description of the problem in the conventional mathematical notation, quite unlike other languages such as "FORTRAN".

Since all data and programs in "APL" must be typed in by the user, it is not reasonable to deal with extensive programs or large sets of data. Similarly for economy of time, display of results should be kept to a minimum, since the typewriter prints only 15 characters per second.

Because of the fact that the volume of our input and output data is moderate the above mentioned insufficiencies of the "APL" are not a problem.

Our program consists of three main units (functions). These are: Input, calculation and output units. Input function consists of sixty statements, and is arbitrarily called "CPF" (Cardio Pulmonary Functions). Calculation function has forty nine statements and is called "ABC". We have two output functions (one intermediary and the other final). They have been called "DISPLAY" and "DISANS" (Display and Answer) respectively. "Display" function contains twelve statements and there are twenty-six statements in "Disans" function. Several statements in the above functions may need some elaboration.

a. <u>The input function (CPF)</u> Following the submission of the input data a matrix with 12 rows and 6 columns consisting of the main components of the data is automatically displayed, the user is also questioned whether he requires correction or not (statement 50). If no typographical mistake is made and the input data is correct, the carriage return key on the console typewriter is depressed and the function is completed. However if corrections are necessary the different input entries requiring correction are identified by their

be measured by the equation:

$$Vt = \frac{VA}{\alpha t} \left[\left(\frac{100}{\text{intercept}} - 1\right)\right] \frac{760}{PB - 47}$$

If the value of the intercept is beyond this range tissue volume will be determined by the prediction equation (statement 31).

Statements 41 to 45 represent prediction equations for body surface area, total lung capacity, pulmonary parenchymal tissue volume, diffusing capacity and pulmonary capillary blood flow respectively as derived by Johnson.[129]

Statements 46 and 49 represent the final and the intermediary output functions and statments 47 and 48 merely separate these two outputs by two blank lines.

c. Intermediary (DISANS) and final output (DISPLAY) are simple and do not require elaboration.

The DISANS function displays all the intermediary results step by step and is particularly helpful in "trouble shooting" in the analysis of the results.

As far as time is concerned, in our hands, it took approximately two and a half hours to prepare the raw data from the spirographic tracings and the chromatograms of each subject. This is fed to the computer as the input data. This phase of data submission takes approximately four minutes. The final and intermediary outputs are typewritten in less than one and three minutes respectively. The actual calculation

appropriate row and column number (statement 54) and the corrected value is substituted (statement 55). After substitution of each new entry a new corrected matrix is displayed and necessary correction may continue in the above stated manner.

b. Calculation Function Statement 21 of this function makes correction of the diffusing capacity for the value of the patient's hemoglobin. According to the following equation.[20]

$$DL_{CO} \text{ corrected} = \left(\left(\frac{15}{Hb} \times 0.5\right) + 0.5\right) \times DL_{CO} \text{ observed}$$

Statement 23 is a new function by which regression line is drawn by the last square technique. The "Y" axis of the coordinates is the reciprocal of corrected diffusing capacity. The "X" axis is the reciprocal of theta which in turn is derived from alveolar oxygen tension according to the following equation:

$$1/\theta = 0.73 + 4.4 \times Po2 \quad [61]$$

Intracorpuscular oxygen tension is approximated substracting "5" mm. Hg. from alveolar 02 tension.[105] Statements 24 and 25 are reciprocals of the intercept and the slope of the regression line respectively. Statement 30 is a conditional statement made prior to the measurement of the pulmonary parenchymal tissue volume (answer 36). If the value of the intercept of acetylene disappearance (D) is between 80 and 98 tissue volume will

performed by the computer is less than a fraction of a second, the time necessary for the same calculation manually takes more than 4-5 hours and usually lacks the computer precision.

The operating procedures for the use of computer are as follow:

1. The typewriter is turned on and the connection with the computer is made by dialling the appropriate number on the telephone set present next to the terminal.
2. User should be recognised by the computer by typing the appropriate number previously allocated to him by the Department of Computing Science.
3. The user should type the name of the input program (CPF), this will retrieve the data which once in advance has been typed. The use has to provide the input data in a systematic matter as arranged previously in the input program. Errors in input data may be deleted at the end of the submission of the input data as was discussed earlier.
4. By typing (DISANS-DISplay ANSwer) all the intermediary steps in the calculation of final results will be typewritten automatically and in a prearranged systematic fashion.
5. By typing the name of the calculation program (ABC) and hitting the carriage return key the output data representing the final results and intermediary steps will be displayed.

Samples of different functions and input and output are represented in the ensuing pages.

```
      ∇CPF[[]]∇
    ∇ CPF;J;B;IN
[1]   'TYPE DATE AND PATIENT NAME'
[2]   INFORM←⍞
[3]   'IS IT FIRST SET OF TRIALS?'
[4]   →(⍞∈'NO')/21
[5]   'AGE'
[6]   AGE←⍞
[7]   AGE←AGE[1]+AGE[2]÷12
[8]   'TYPE WT'
[9]   WT←⍞
[10]  'HT'
[11]  HT←⍞
[12]  'PB'
[13]  PB←⍞
[14]  'STPD FACTOR'
[15]  STPD←⍞
[16]  'TYPE LOW AND HIGH TO2 IN PERCENT'
[17]  TO2←⍞
[18]  ' TYPE HEMOGLOBIN'
[19]  HB←⍞
[20]  A←(12 6)⍴0
[21]  'GAS IN BAG FOR EXPTS 1-4'
[22]  A[⍳5;1]←⍞
[23]  'GAS IN BAG FOR EXPTS 5-6'
[24]  A[⍳5;5]←⍞
[25]  J←2
[26]  D4:A[⍳5;J]←A[⍳5;1]
[27]  →(5>I←J+1)/D4
[28]  A[⍳5;6]←A[⍳5;5]
[29]  J←1
[30]  D1:('EXPT ';J)
[31]  ' ALVEOLI ME,O2,FEV1,CO,C2H2'
[32]  A[6 7 8 9 10 ;J]←⍞
[33]  'RHT'
[34]  A[11;J]←⍞
[35]  'VI'
[36]  A[12;J]←⍞
[37]  →(6≥J←J+1)/D1
[38]  D2:('MEB    ';A[1;])
[39]  ('O2B    ';A[2;])
[40]  ('N2B    ';A[3;])
[41]  ('COB    ';A[4;])
[42]  ('C2H2B  ';A[5;])
[43]  ('MEA    ';A[6;])
[44]  ('O2A    ';A[7;])
[45]  ('FEV1   ';A[8;])
[46]  ('COA    ';A[9;])
[47]  ('C2H2A  ';A[10;])
[48]  ('RHT    ';A[11;])
[49]  ('VI     ';A[12;])
[50]  'DO YOU REQUIRE CORRECTIONS ?'
[51]  B←⍞
[52]  →(∨/B∈'Y')/0
[53]  D3:'GIVE ROW AND COLUMN NUMBER'
[54]  IN←⍞
[55]  'GIVE CORRECTED VALUES '
[56]  A[IN[1];IN[2]]←⍞
[57]  'ARE MORE CORRECTIONS NECESSARY ?'
[58]  B←⍞
[59]  →(∨/B∈'N')/D2
[60]  →D3
      ∇
```

INPUT FUNCTION

∇*ABC*[□]∇

CALCULATION FUNCTION

```
     ∇ ABC
[1]    ANS←(62 6)ρ0
[2]    T←1
[3]    A1:ANS[8;T]←A[12;T]×STPD
[4]    ANS[9;T]←(ANS[8;T]×A[1;T]÷A[6;T])-85
[5]    ANS[10;T]←ANS[9;T]-ANS[8;T]
[6]    ANS[11;T]←ANS[10;T]×1.21
[7]    ANS[12;T]←A[6;T]÷A[1;T]
[8]    ANS[13;T]←ANS[12;T]×A[4;T]
[9]    ANS[14;T]←ANS[12;T]×A[5;T]
[10]   ANS[15;T]←A[9;T]÷ANS[13;T]
[11]   ANS[16;T]←A[10;T]÷ANS[14;T]
[12]   ANS[17;T]←ANS[13;T]÷A[9;T]
[13]   ANS[18;T]←ANS[14;T]÷A[10;T]
[14]   ANS[19;T]←A[11;T]
[15]   ANS[20;T]←TO2[1+(T>4)]×A[7;T]÷A[2;T]
[16]   ANS[21;T]←ANS[20;T]×(PB-47)÷100
[17]   ANS[25;T]←ANS[9;T]×60÷PB-47
[18]   ANS[26;T]←ANS[25;T]÷A[11;T]
[19]   ANS[27;T]←(⊙ANS[17;T])
[20]   ANS[28;T]←ANS[26;T]×ANS[27;T]
[21]   ANS[28;T]←(0.5+15×0.5÷HB)×ANS[28;T]
[22]   →(6≥T←T+1)/A1
[23]   RESULT←(0.73+4.4×(ANS[21;]-5)÷760)SLOPE(÷ANS[28;])
[24]   DM←÷RESULT[2]
[25]   VC←÷RESULT[1]
[26]   RESULT←ANS[19;⍳4]SLOPE(ANS[16;⍳4])
[27]   RESULT[2]←RESULT[2]
[28]   ANS[36;⍳4]←ANS[9;⍳4]÷0.768
[29]   D←RESULT[2]×100
[30]   →((D>80)∧D<98)/L1
[31]   ANS[40;⍳4]←0.1417×0.01934×HT*3
[32]   →L2
[33]   L1:R←(100÷D)-1
[34]   C←760÷PB-47
[35]   ANS[40;⍳4]←ANS[36;⍳4]×R×C
[36]   L2:VT←(+/ANS[40;⍳4])÷4
[37]   ANS[41;1]←(+/ANS[9;]÷6)
[38]   ANS[42;1]←ANS[41;1]÷ANS[41;1]+(PB-47)×0.768×VT÷760
[39]   ANS[43;1]←-ANS[41;1]×760×60÷0.74×ANS[42;1]×(PB-47)
[40]   ANS[44;1]←|ANS[43;1]×RESULT[1]
[41]   BSA←((WT×0.4536)*0.425)×((HT×2.54)*0.725)×0.007184
[42]   PTLC←0.01934×(HT*3)
[43]   PTV←0.1417×PTLC
[44]   PDL←25-(0.117×AGE)
[45]   PQC←3100×BSA
[46]   DISPLAY
[47]   ' '
[48]   ' '
[49]   DISANS
     ∇
```

```
      ∇DISPLAY[⎕]∇
```

```
     ∇ DISPLAY                                    FINAL OUTPUT FUNCTION
[1]    INFORM
[2]    ('DL    ';ANS[28;])
[3]    ('AVERAGE DL    ';(((+/ANS[28;⍳4])÷4),(+/ANS[28; 5 6])÷2))
[4]    ('DM    ';DM)
[5]    ('VC    ';VC)
[6]    ('FEV1    ';(+/A[8;])÷6)
[7]    ('VT    ';(+/ANS[40;⍳4]÷4))
[8]    ('QC    ';ANS[44;1])
[9]    ('RSA    ';RSA)
[10]   ('PTLC    ';PTLC)
[11]   ('PTV    ';PTV)
[12]   ('PDL    ';PDL)
     ∇
```

```
      ∇DISANS[⎕]∇
```

```
     ∇ DISANS
[1]    ('8     ';ANS[8;])
[2]    ('9     ';ANS[9;])
[3]    ('10    ';ANS[10;])                   INTERMEDIARY OUTPUT FUNCTION
[4]    ('11    ';ANS[11;])
[5]    ('12    ';ANS[12;])
[6]    ('13    ';ANS[13;])
[7]    ('14    ';ANS[14;⍳4])
[8]    ('15    ';ANS[15;])
[9]    ('16    ';ANS[16;⍳4])
[10]   ('17    ';ANS[17;])
[11]   ('18    ';ANS[18;⍳4])
[12]   ('19    ';ANS[19;])
[13]   ('20    ';ANS[20;])
[14]   ('21    ';ANS[21;])
[15]   ('ABS     ';0.73+4.4×(ANS[21;]-5)÷760)
[16]   ('25    ';ANS[25;])
[17]   ('26    ';ANS[26;])
[18]   ('27    ';ANS[27;])
[19]   ('28    ';ANS[28;])
[20]   ('ORD    ';÷ANS[28;])
[21]   ('36    ';ANS[36;⍳4])
[22]   ('40    ';ANS[40;⍳4])
[23]   ('41    ';ANS[41;1])
[24]   ('42    ';ANS[42;1])
[25]   ('43    ';ANS[43;1])
[26]   ('44    ';ANS[44;1])
     ∇
```

```
ANS[8]:INSPIRATORY VOLUME(VI)
ANS[9]:ALVEOLAR VOLUME(VA)
ANS[10]:RESIDUAL VOLUME(VR STPD)
ANS[11]:RESIDUAL VOLUME(VR BTPS)
ANS[12]:ALVEOLAR NEON÷BAG NEON
ANS[13]:INITIAL CARBON MONOXIDE CONCENTRATION(FACO.0)
ANS[14]:INITIAL ACETYLENE CONCENTRATION(FAC2H2.0)
ANS[15]:FACO.T÷FACO.0
ANS[16]:FAC2H2.T÷FAC2H2.0
ANS[17]:FACO.0÷FACO.T
ANS[18]:FAC2H2.0÷FAC2H2.T
ANS[19]:BREATH HOLDING TIME(ΔT)
ANS[20]:ALVEOLAR OXYGEN CONCENTRATION(FAO2 )
ANS[21]:ALVEOLAR OXYGEN TENSION(PAO2)
ABS:RECIPROCAL OF THETA
ANS[25]:VA×60÷PB-47
ANS[26]:ANS[25]÷ΔT
ANS[27]:NATURAL LOG ANS[27]
ANS[28]:PULMONARY DIFFUSING CAPACITY
ORD:RECIPROCAL OF DLCO
ANS[36]:ALVEOLAR VOLUME÷0.768
ANS[40]:PULMONARY PARENCHYMAL TISSUE VOLUME(VT)
ANS[41]:AVERAGE ALVEOLAR VOLUME(AVERAGE VA STPD)
ANS[42]:ANS[41]÷ANS[41]+(PB-47)×0.868×VT÷760
ANS[43]:ANS[41]×760×60÷0.740×ANS[42]×(PB-47)
ANS[44]:ANS[43]×SLOPE OF C2H2 DISAPPEARANCE
```

RESULT CODE

RAW DATA AND

INPUT FUNCTION

```
      CPF
TYPE DATE AND PATIENT NAME
A.R.ESFANDIARY MAY 8,1968 PRIOR TO MEDICATION
IS IT FIRST SET OF TRIALS?
YES
AGE
□:
      29 8
TYPE WT
□:
      145
HT
□:
      71
PR
□:
      710
STPD FACTOR
□:
      0.832
TYPE LOW AND HIGH TO2 IN PERCENT
□:
      20.4,95
 TYPE HEMOGLOBIN
□:
      15
GAS IN BAG FOR EXPTS 1-4
□:
      232.5,243,0,153,130
GAS IN BAG FOR EXPTS 5-6
□:
      248.5,2 27,0,176.5,0
EXPT 1
 ALVEOLI NE,O2,FEV1,CO,C2H2
□:
      162 .5,219,2910,62 .5,78
BHT
□:
      6.87
VI
□:
      4697
EXPT 2
 ALVEOLI NE,O2,FEV1,CO,C2H2
□:
      163,212,2910,59,77
BHT
□:
      7.69
VI
□:
      4292
EXPT 3
 ALVEOLI NE,O2,FEV1,CO,C2H2
□:
      159,209,2868,48,77
BHT
□:
      10.22
VI
□:
      4333
```

```
EXPT 4
 ALVEOLI NE,O2,FEV1,CO,C2H2
[]:
      169,215,2394,61,75
BHT
[]:
      8
VI
[]:
      4457
EXPT 5
 ALVEOLI NE,O2,FEV1,CO,C2H2
[]:
      171,213,2683,81,0
BHT
[]:
      8.78
VI
[]:
      4003
EXPT 6
 ALVEOLI NE,O2,FEV1,CO,C2H2
[]:
      146,219,2868,77,0
BHT
[]:
      8.22
VI
[]:
      3631
NEB    232.5  232.5  232.5  232.5  248.5  248.5
O2B    243  243  243  243  227  227
N2B    0  0  0  0  0  0
COB    153  153  153  153  176.5  176.5
C2H2B 130  130  130  130  0  0
NEA    162.5  163  159  169  171  146
O2A    219  212  209  215  213  219
FEV1   2910  2910  2868  2394  2683  2868
COA    62.5  59  48  61  81  77
C2H2A 78  77  77  75  0  0
BHT    6.87  7.69  10.22  8  8.78  8.22
VI     4697  4292  4333  4457  4003  3631
DO YOU REQUIRE CORRECTIONS ?
NO
```

ABC

A.R.ESFANDIARY MAY 8,1968 *PRIOR TO MEDICATION*
DL 38.95504062 35.23289723 35.7883941 34.0814782 19.85370594 16.57289132
AVERAGE DL 36.01445254 18.21329863
DM 71.46684315
VC 100.6668641
*FEV*1 2772.166667
VT 980.8472215
QC 3038.409279
BSA 1.839503068
PTLC 6921.99874
PTV 980.8472215
PDL 21.529

8 3907.904 3570.944 3605.056 3708.224 3330.496 3020.992
9 5506.3088 5008.524417 5186.544151 5016.550769 4754.931322 5056.893918
10 1598.4048 1437.580417 1581.488151 1308.326769 1424.435322 2035.901918
11 1934.069808 1739.472305 1913.600663 1583.075391 1723.566739 2463.441321
12 0.6989247312 0.7010752688 0.6838709677 0.7268817204 0.6881287726 0.5875251509
13 106.9354839 107.2645161 104.6322581 111.2129032 121.4547284 103.6981891
14 90.86021505 91.13978495 88.90322581 94.49462366
15 0.5844645551 0.5500421027 0.4587495376 0.5484975055 0.6669151633 0.7425394854
16 0.8584615385 0.8448560642 0.8661103048 0.793695949
17 1.710967742 1.818042646 2.17983871 1.823162348 1.499441091 1.346729729
18 1.164874552 1.183633571 1.154587348 1.259928315
19 6.87 7.69 10.22 8 8.78 8.22
20 18.38518519 17.79753086 17.54567901 18.04938272 89.14096916 91.65198238
21 121.8937778 117.9976296 116.3278519 119.6674074 591.0046256 607.6526432
ABS 1.40675345 1.384196803 1.374529669 1.393863938 4.122658358 4.219041618
25 498.3084887 453.2601283 469.3705114 453.986495 430.3105268 457.6374586
26 72.53398671 58.94149912 45.92666452 56.74831187 49.01031057 55.67365677
27 0.5370591414 0.5977604533 0.7792508877 0.6005725471 0.4050924327 0.2976792307
28 38.95504062 35.23289723 35.7883941 34.0814782 19.85370594 16.57289132
ORD 0.02567061885 0.02838256512 0.02794201934 0.02934145033 0.05036843012 0.06033950147
36 7169.672917 6521.516168 6753.312697 6531.967147
40 980.8472215 980.8472215 980.8472215 980.8472215
41 5088.292229
42 0.8856228455
43 534001.933
44 3038.409279

FINAL OUTPUT

APPENDIX D

STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

Means and standard deviations were calculated using conventional technique of measurement applied to small samples. Standard deviation was determined by taking the square root of the sum of squared deviations from the mean divided by N-1, where N is the number of observations. In the following computer program N, M, V and SD respectively represent the number of observations, mean, variance and the standard deviation of the sample.

X is a vector consisting of N variables. After submission of data in the form of a vector; then, by typing the function name "MVSD X" and hitting the carriage return, four values will be immediately and automatically displayed, which respectively represent N,M,V and SD.

```
      ∇MVSD[□]∇

     ∇ R←MVSD X
[1]    N←⍴X
[2]    M←(+/X)÷N
[3]    V←(+/(X-M)*2)÷N-1
[4]    SD←V*0.5
[5]    R←N,M,V,SD
     ∇
```

"t" values for the determination of "P" were computed using the following program in "APL"

```
      ∇TEST[□]∇

     ∇ X TEST Y;G
[1]    G←(((X[3]-1)×X[2]*2)+(Y[3]-1)×Y[2]*2)÷X[3]+Y[3]-2
[2]    (X[1]-Y[1])÷((G÷X[3])+G÷Y[3])*0.5
     ∇
```

Where:

G represents pooled standard deviation (squared)

X and Y are vectors, each consisting of three variables representing mean, standard deviation and number of observations respectively.

X (1) : mean of x

X (2) : standard deviation of X

X (3) : number of observation of X

Y (1) : mean of Y

Y (2) : standard deviation of Y

Y (3) : number of observation of Y

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